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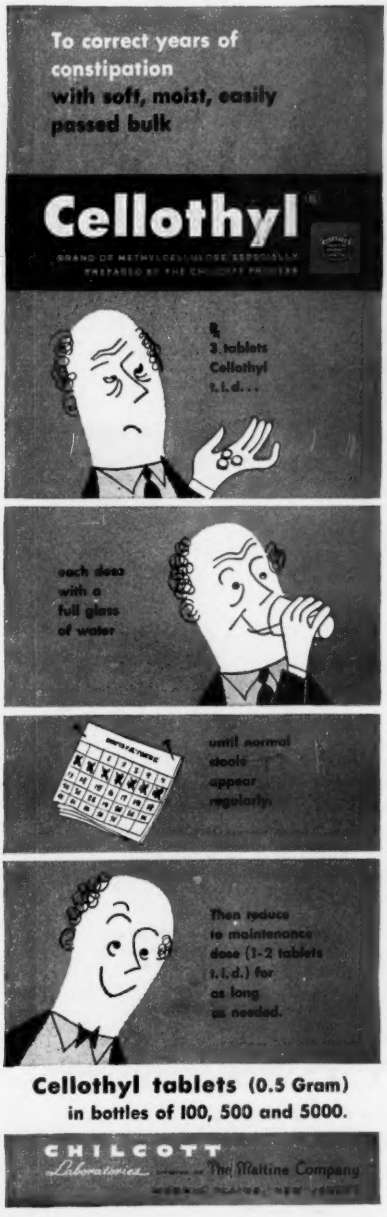
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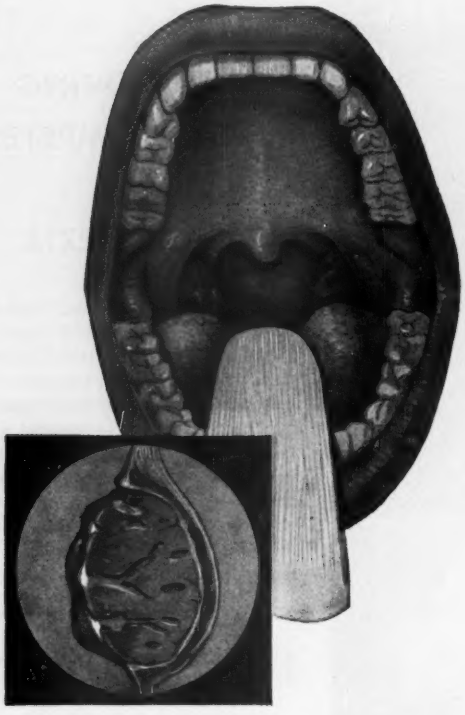
1. Newey, J. A., and Goetzl, F. R.: Permanente Med. Bull. 7:67 (July) 1949.



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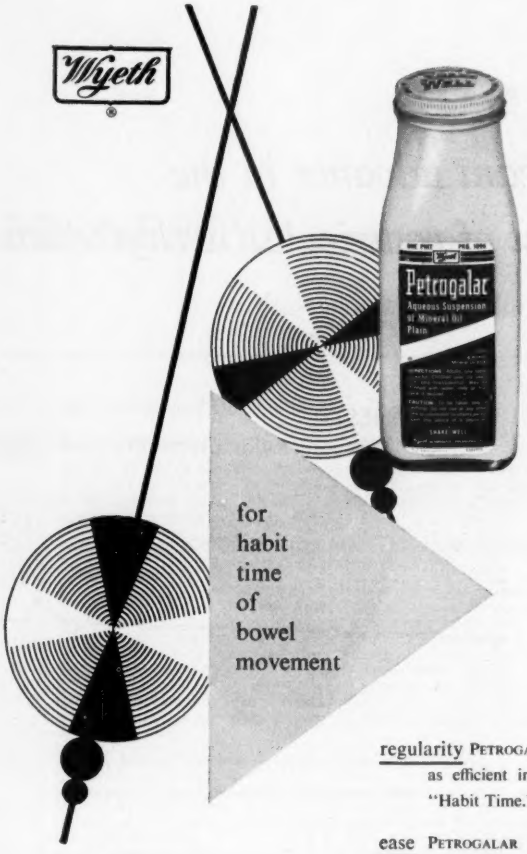

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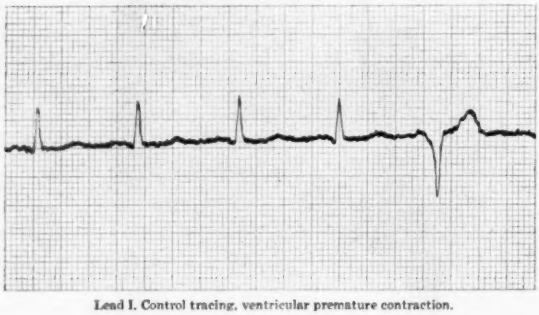
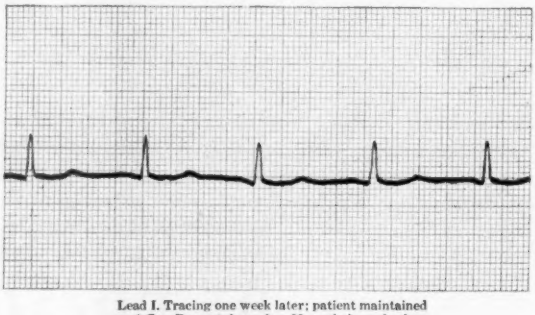


Lead I. Control tracing, ventricular premature contraction.



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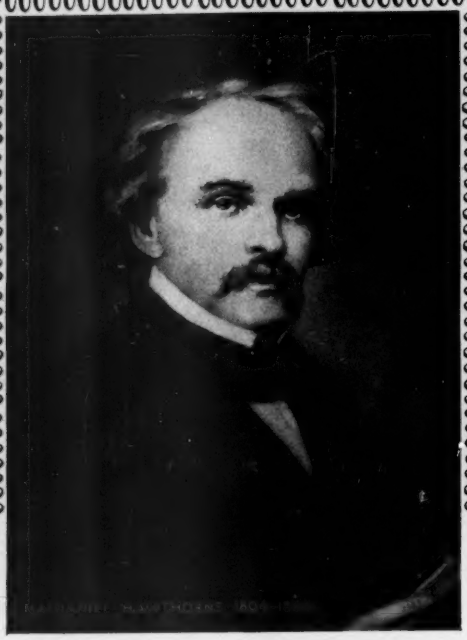

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Volume 245 OCTOBER 25, 1951 Number 17

THE USE OF PROPYLTHIOURACIL IN HYPERTHYROIDISM AND DIABETES*

A Study of Forty-One Cases

BYRON D. BOWEN, M.D.,† AND ALFRED R. LENZNER, M.D.‡

BUFFALO, NEW YORK

OVERT diabetes frequently masks coexistent hyperthyroidism. Instances of this dynamic combination have occasionally escaped early recognition, even by physicians most of whose patients are diabetics. Its treatment often entails larger-than-average doses of antithyroid medication, not only to establish control but also to maintain it. During the past four years we have studied 41 hyperthyroid diabetics. It is our purpose to re-evaluate the combination of hyperthyroidism and diabetes, to note the effectiveness of propylthiouracil in achieving early control and to determine the practicability of maintaining antithyroid therapy over extended periods of time.

Observers from three clinics in the United States agree that the frequency of diabetes is increased in hyperthyroidism from any cause. The comparative frequency of diabetes in primary (exophthalmic and hyperplastic) hyperthyroidism and in secondary (adenomatous) hyperthyroidism is enlightening. Regan and Wilder,[1] at the Mayo Clinic, noted that of 5253 patients with primary hyperthyroidism operated on from 1923 to 1937, 99 had diabetes, an incidence of only 1.9 per cent. During this same period, however, 3.5 per cent with adenomatous goiter had diabetes. In a second period (1935-1937) they noted 1131 instances of exophthalmic goiter and 1882 cases of toxic adenomatous goiter. In the former, 1.7 per cent had diabetes, but in the latter 5.6 per cent had diabetes. In other words, diabetes was three times more frequent in toxic goiter of the adenomatous variety. The control incidence of patients admitted without hyperthyroidism was 1.7 per cent, the approximate figure pointed up by recent diabetic surveys. A second report is that of John,[2] who wrote extensively on this subject. Diabetes was present in 2.3 per cent of patients with hyperthyroidism at the Cleveland Clinic. In contrast to the experience in the Mayo Clinic, Joslin and Lahey[3, 4] reported 150 diabetics with primary hyperthyroidism to 1946 but only 105 diabetics with secondary hyperthyroidism during the same period.

The reason for the preponderance of primary hyperthyroidism in the Boston group is probably related to its geographical location in New England. The patients in the other two groups came mostly from the great Lakes section—the so-called "Goiter Belt." Our patients likewise are drawn from this "Goiter Belt." However, it is not our purpose to study the frequency of hyperthyroidism with diabetes, but to examine this combination as it exists and to determine the efficacy of methods for its temporary and permanent control.

TECHNIC OF STUDY

In the majority of the 41 diabetics presented in this study there was no difficulty in confirming a presenting diagnosis of hyperthyroidism. There were one or more of the usual findings of nervousness, weight loss, increase in appetite, tachycardia and wide pulse pressure. In addition, the symptoms of active diabetes were usually exhibited. Thyroid hypertrophy was not always present, however. In questionable cases a diagnostic trial was made with antithyroid medication. Large doses of propylthiouracil§ were given daily for a period of three to six weeks. If the basal metabolic rate dropped to normal, the drug was promptly stopped and withheld for a similar period. If the basal metabolic rate rose again, it was concluded that the patient was also hyperthyroid. This response was correlated with the weight curve — to us an important criterion of good diabetic control. The following case illustrates this diagnostic test in a patient with an adenoma of suspected toxicity.

CASE REPORT

CASE 1. A 48-year-old man developed active diabetes, marked by a 30-lb. weight loss over a 4-month period in 1946. The diabetes was stabilized by diet and 10 units of protamine zinc insulin daily, the fasting blood-glucose level being 141 mg. per 100 cc. The pulse was 76 and the blood pressure

*From the Diabetic Clinic, Buffalo General Hospital, and the Department of Medicine, University of Buffalo School of Medicine.

†Professor of clinical medicine, University of Buffalo School of Medicine.

‡Instructor in medicine, University of Buffalo School of Medicine.

§Courtesy of the Lederle Laboratories and Eli Lilly and Company.

115/80. Nevertheless, he complained persistently of inanition, sensitivity to heat and excitability. The skin was warm and moist. A walnut-sized solitary nodule was present in the right lobe of the thyroid gland. The basal metabolic rate was +24 initially. One month after he was given propylthiouracil, 100 mg. daily, the basal metabolic rate had fallen to +7 per cent. Later, at the end of 6 weeks without propylthiouracil, the basal metabolic rate had risen from +1 to +18 and the pulse from 80 to 90; he had lost 5 lb. The maintenance dose was then established at 150 mg. daily. On this the subjective response was excellent. Insulin was discontinued, and the patient gained 10 lb. After 14 months on propylthiouracil, increasing enlargement of the thyroid nodule became evident. The dose was maintained at 100 mg. of propylthiouracil daily. Nevertheless, thyroidectomy was refused until thirty-six months after antithyroid therapy had been started. The operation was successful. The patient is now on a controlled diet and the improvement has been sustained.

Sex Distribution

Distribution was approximately equal in the hyperplastic hyperthyroid group — 6 women and 5 men. In the adenomatous group, however, 25 of 29 patients, or 85 per cent, were women. In addition, the one case of Riedel's struma occurred in a female.

Age Distribution

In the hyperplastic group the mean age at the commencement of treatment was forty-eight years. The youngest patient, a woman, was twenty-two years of age. The remainder were over thirty-five, the oldest being sixty-five years of age. In the adenomatous group of 29 patients ranging from forty-three to eighty-four years of age, the mean age at the commencement of therapy was sixty years. Adenomatous hyperthyroidism, therefore, manifested itself in the diabetics in this series at a later age than did hyperplastic hyperthyroidism.

Duration of Hyperthyroidism

Among the hyperplastic goiters, it was possible to date the onset of the hyperthyroid state in 8 of the 11 patients. For 6 of these 8 patients the duration of hyperthyroidism prior to treatment ranged close to a mean of two years. A seventh patient had recurrent hyperplastic hyperthyroidism twenty-nine years after thyroidectomy. The eighth patient had refused thyroidectomy nine years previously, after an excellent response to iodine therapy. Four years ago as much as 900 mg. of thiouracil and later 800 mg. of propylthiouracil had failed to control satisfactorily the hyperthyroidism. Thyroidectomy was eminently successful.

Of the 29 patients with adenomatous goiters, it was possible to date the onset of the hyperthyroid state in only 14. Among these, one case dated back twenty years and another thirteen years. The average duration of hyperthyroidism among the remaining 12 patients was 2.8 years. The patients had all been hyperthyroid for less than five years.

From these data it may be inferred that in diabetic patients primary hyperthyroidism is recognized earlier than the adenomatous or secondary variety.

Family History of Diabetes

A family history of diabetes was found by Joslin[8] in 52 per cent of his hyperthyroid patients. In our similar but smaller group of patients with hyperplastic glands we found that 6 of 11 patients, or 55 per cent, had a family history of diabetes. In the 30 patients with adenomatous goiter 12, or 40 per cent, had positive family histories. These data have been recently checked, by either mail or personal communication. This incidence of family history is significantly higher than the 6.7 per cent positive history in the general diabetic population and the 1.2 per cent family history in the nondiabetic population (Joslin).

Dosage of Propylthiouracil

We have found that comparatively large doses of propylthiouracil are necessary to establish control of the hyperthyroid state in diabetics. Dosages of from 600 to 800 mg. daily were commonly given during the first few weeks of treatment. Four patients were unsatisfactorily controlled prior to thyroidectomy, even with 600 mg. or more of propylthiouracil daily. The following case illustrates hyperthyroidism refractory to propylthiouracil encountered in several patients:

Case 2. A 78-year-old woman had been hospitalized in 1942 with diabetic coma. A large colloid adenoma had been noted, but the basal metabolic rate was +10. The insulin requirement was 54 units daily in protamine form. In 1946, after recovery from a second episode of coma, her basal metabolic rate was +60. The patient was both difficult to control diabetically and resistant to antithyroid therapy. As much as 800 mg. of thiouracil or propylthiouracil was given daily for long periods, but at no time did the basal metabolic rate fall below +20 per cent. Nevertheless, she did gain weight from 95 to 122 pounds, with much clinical improvement.

In 1948 she finally consented to thyroidectomy, which was accomplished after iodine preparation. The final diet was 1900 calories and the insulin requirement identical with that before the onset of hyperthyroidism — 54 units daily. Microscopically, most of the colloid nodules showed central regressive changes with hyalinization. No areas of hyperplasia were shown.

However, the great majority of patients were easily brought under control with adequate dosage of propylthiouracil. We chose to keep the basal metabolic rate between 0 and +10 per cent. No cases of induced hypothyroidism were noted prior to operation.

Reactions to Propylthiouracil

There were no serious reactions to the propylthiouracil. One case each of transitory granulocytopenia, urticaria and acute thyroiditis were either consequent to or coincident with propylthiouracil therapy. A complete remission of the hyperthyroidism for more than a year occurred in 4 patients. It was possible to stop propylthiouracil for several months in 2 cases before relapse occurred. Propyl-

thiouracil therapy was then necessary in fairly large dosage. In accord with the experience of other physicians, the development of nodules or further enlargement of those already present has occurred in several patients. This was not particularly associated with large dosages of the drug but seemed to be related to the duration of treatment

Effect of Treatment on Caloric and Insulin Requirement

The caloric requirement after thyroidectomy did not vary greatly from that of the drug-controlled hyperthyroid state prior to operation. Concomitantly, there was little if any change in the insulin requirement before and after operation. The case history cited above is representative of the group in this regard. Only one patient required a gradual increase of insulin from 54 to 92 units. In general, the belief of Thorn[6] is supported — namely, that when the insulin requirement decreases it is associated with reduction in the caloric intake. The following account is illustrative of the constancy in the insulin and dietary requirements.

Case 3. A 67-year-old woman first learned that she had diabetes in 1940. A sister, a cousin and a maternal aunt were likewise diabetic. Her weight was 151 pounds in 1940. In July, 1947, she noted an inordinate weight loss (25 pounds), a warm moist skin, nervousness, easy fatigability and a pulse of 90. The thyroid gland was not enlarged. The basal metabolic rate was +40 per cent; it required 15 months to reduce the basal metabolic rate to — 9 per cent, the propylthiouracil dosage during this period being as high as 600 mg. daily. The propylthiouracil intake could not be reduced to less than 300 mg. daily.

Two years after propylthiouracil had been started a walnut-sized nodule was found in the right lobe of the thyroid gland. The basal metabolic rate was +9 per cent, the pulse 72; her diet was 1750 calories daily and her insulin dosage 28 units daily, with 450 mg. of propylthiouracil daily. She weighed 123 pounds.

Thyroidectomy revealed an adherent bilateral, multiple nodular goiter with distinct hyperplasia.

Her present weight, 8 months after operation, is 123 pounds; her diet is 1750 calories and her insulin dosage 28 units daily.

Table 1. *Pertinent Data on 17 Adenomatous Hyperthyroid Patients.*

Case No.	Age	Sex	Duration of Diabetes	Duration of Hyperthyroidism	Weight			Deviation in Normal Surface Area		Basal Metabolic Rate		Maintenance Dose	
					Low	High	Ideal			First	Last	Propylthiouracil	Insulin
			yr.	yr.	lb.	lb.	lb.			%	%	mg.	units
1	65	F	6	?	77	112	131	4'11"	+12%	+47	+12	150	60p 30
2	69	F	2	13	90	104	142	5'3"	0	+49	+5	200	24
3	76	F	7	5	96	116	133	5'0"	+1%	+63	+15	400	42p 20
4	66	M	10	?	127	250	163	5'8"	+20%	+22	−2	200	40
5	62	F	11	5	113	250	136	5'1"	+29%	+43	−1	400	30
6	75	F	35	2	126	290	144	5'4"	+33%	+40	+8	200	40p 12
7	55	F	15	?	134	182	141	5'3"	+12%	+35	−2	800	28
8	62	F	10	3	145	174	148	5'5"	+30%	+37	+6	200	40
9	69	F	3	3	121	130	133	5'0"	+8%	+26	+16	300	22p 10
10	69	F	21	2	103	130	142	5'3"	+8%	+27	−8	150	50p 10
												0	
11	49	M	2.5	2.5	157	167	137	5'2"	+15%	+24	+8	150	0
12	84	F	2	2	110	122	137	5'2"	−1%	+16	−16	200	30
13	58	F	7	4	126	135	139	5'2"	+10%	+44	+3	50	30
14	65	F	8	1	126	129	142	5'4"	+5%	+40	+3	600	30
15	45	F	2	1.5	113	150	132	5'3"	+12%	+32	−9	150	32
16	78	M	31	3	132	205	163	5'8"	+10%	+29	0	200	18
17	60	F	10	?	95	160	131	4'11"	+8%	+39	+14	400	42
18	62	F	12	1.5	118	150	141	5'3"	+2%	+39	+29	600	80
19	57	F	12	?	161	228	128	5'3"	+25%	+80	+12	600	15
20	63	F	3	?	113	140	137	5'2"	+1%	+27	+2	400	26p 16
												0	
21	79	F	6	20	140	202	141	5'3"	+17%	+22	+1	200	40
												0	
22	62	F	2	?	102	160	128	4'10"	+9%	+25	+15	400	30
23	62	F	—	?	100	180	141	5'3"	+11%	+68	+8	400	30
24	57	F	12	?	104	125	133	5'0"	−2%	+28	+10	250	0
25	57	M	0.5	?	146	180	158	5'7"	+6%	+15	−1	150	0
26	71	F	4.5	?	93	132	131	4'11"	−1%	+27	−12	300	36p 18
27	61	F	9	1	115	178	133	5'0"	+15%	+34	+10	300	22
28	43	F	0.1	?	149	183	138	5'3"	+12%	+23	+9	400	0
29	55	F	3	3?	105	128	135	5'1"	−2%	+22.5	0	150	26

This account illustrates the diabetic family history, the development of thyroid hyperplasia on the large dose of propylthiouracil found necessary in this case and the constancy of dietary and insulin requirements before and after operation.

Discussion

The precise relation between hyperthyroidism and diabetes is as yet only partially determined. When hyperthyroidism precedes diabetes there is abundant explanation for the increased incidence of diabetes. The syndrome in this instance is probably a result of multiple hormonal action, rapid carbohydrate absorption and increased caloric intake. Houssay[7] and his co-workers have studied this problem. They were able to produce irreversible (metathyroid) diabetes by feeding thyroid

extract to animals prepared by partial pancreatectomy or by subdiabetogenic doses of Alloxan. Conversely, Martinez[8] observed that thiouracil delayed the onset of diabetes after subtotal pancreatectomy in rats, although the effect was not so complete as that following thyroidectomy. Later, Houssay and Martinez noted several cures of mild Alloxan diabetes with thiouracil. From this one may infer that the increased demands of hyperthyroidism alone could convert a latent pancreatic insufficiency into overt diabetes. It is doubtful, however, that diabetes would result in a previously nondiabetic subject.

Shipner[9] made the interesting observation that 6 dogs from which he had removed 19/20 of the glucose level within three hours. Despite this evidence against (complete) failure of utilization, a semblance of balance is restored only with insulin. This balance is unstable, however, and we have found that antithyroid therapy is almost always mandatory for permanent stabilization in the hyperthyroid diabetic.

When diabetes precedes the hyperthyroidism, however, as in most of the cases in this series, the pathogenesis is obscure. Diabetes should not hasten the development of hyperthyroidism — at least not by any known mechanism. Nevertheless, among 25,148 true diabetic patients Joslin has reported a twofold to threefold increased incidence (1 per cent) of hyperthyroidism. It seemed to us

TABLE 2. *Pertinent Data on 12 Hyperplastic Hyperthyroid Patients.*

Case No.	Age	Sex	Duration of Diabetes	Duration of Hyperthyroidism	Weight			Deviation in Normal Surface Area		Basal Metabolic Rate		Maintenance Dose	
					Low	High	Ideal			First	Last	Propylthiouracil	Insulin
			yr.	yr.	lb.	lb.	lb.		%	%	%	mg.	units
30	60	F	8	3	83	105	135	5'1"	−6	+19	−12	125	30
31	55	M	8	2	130	154	162	5'8"	−2	+53	+11	300	60p 10
32	44	F	21	?	108	114	131	5'1"	−3	+37	+45	500	16-0-18-0
33	49	F	7	2	140	152	142	5'3"	+2	+35	+4	200	38p 18
34	50	F	6	29	85	116	144	5'4"	−10	+16	+12	100	68p 34
35	52	M	—	4	113	228	184	6'0"	+10	+52	+18	200	50
36	59	M	12	9	132	148	168	5'9"	−4	+41	+5	900	28
37	35	M	2	?	132	172	160	5'9"	+3	+30	−29	400	40
38	35	F	18	0.5	131	140	149	5'8"	+3	+42	+8	400	30p 10
39	22	F	1½	0.8	113	121	138	5'7"	+1	+62	+10	400	52
40	65	M	12	?	98	110	142	5'3"	+1	+52	−1	300	26p 10
41	32	F	4	4	81	115	124	5'2"	−4	+65	+14	50	24p 8

pancreas exhibited voracious appetite. Subtotal pancreatectomy alone had apparently resulted in an increase in caloric intake. Allen[10] had originally noted that if a small fragment of pancreas was left intact in dogs overfeeding made them diabetic. Starvation or undernutrition either insured against diabetes or greatly modified it, depending on the size of the intact fragment. This observation has a clinical counterpart, as a restricted caloric intake operates similarly in patients with obesity and in patients with an increased basal metabolic rate. The one is tantamount to the other.

On the other hand, the dietary intake in the fully developed hyperthyroid state is often enormous. It is apparent that in hyperthyroidism gluconeogenesis from exogenous and endogenous sources supplements the increase in caloric intake. Experimentally, at least, adrenal hypersecretion follows the administration of excessive doses of thyroid hormone. In addition, alimentation is augmented qualitatively and quantitatively.

And yet, as Thorn and Forsham[6] point out, failure of glucose utilization does not occur. Oral glucose ingestion demonstrates elevation of the respiratory quotient with the blood glucose, a normal fall in serum inorganic phosphorus and fall to a normal

unusual that stoutness was the rule among our adenomatous patients whose diabetes preceded their hyperthyroidism. Seventy-one per cent had had surface areas that exceeded normal expectancy, based on the maximum allowable weight at the age when they were heaviest. One may envisage the following sequence: First, varying degrees of stoutness prevail. Secondly, there is a chronic, often varying demand for increased calories, caused by an active adenoma. In addition, the family history frequently confirms a diabetic anlage.

The association of diabetes apparently varies with hyperplastic and adenomatous hyperthyroidism. The Mayo Clinic data imply that a hyperfunctioning adenoma greatly favors the occurrence of diabetes in the Great Lakes area. Exophthalmic goiter apparently carries no significance in this regard. It must be remembered, however, that not only do thyroid nodules vary in frequency from 4 to 10 per cent[11] in the Great Lakes area but also diabetes itself has its greatest incidence, generally, in this same age group, the fifth and sixth decades. The hyperplastic group is younger by approximately two decades; the frequency of diabetes would, therefore, be less in this group. It is possible, however, that the strain of adenomatous hyperthyroid-

ism is more intermittent, more prolonged and more easily overlooked than that which operates in the dynamic syndrome of exophthalmic goiter. This more subtle hyperthyroidism is often completely overshadowed by the diabetes and may go unrecognized for years. The patient continues to lose weight slowly despite adequate caloric intake and satisfactory insulin control. The textbook symptomatology of hyperthyroidism is frequently absent, and palpable enlargement of the thyroid gland often cannot be demonstrated. The basal metabolism is increased, however, and the response to antithyroid therapy is gratifying.

Conclusions

A family history of diabetes was found in 55 per cent of 11 patients with hyperplastic thyroid glands and in 40 per cent of 29 patients with adenomatous goiters.

Stoutness prevailed among those patients whose diabetes was discovered before their hyperthyroidism. This was especially true of those having adenomatous hyperthyroidism.

The most helpful clinical indication of the hyperthyroidism was failure to gain weight while on an adequate diet when the diabetes was controlled. In such cases the diagnostic test with propylthiouracil proved a most helpful adjunct.

The average maintenance dose given the 11 patients with hyperplastic thyrotoxicosis was 350 mg. of propylthiouracil daily. Five of these patients required 600 mg. or more daily for maintenance of control. The average maintenance dose of propylthiouracil given the 29 patients with adenomatous thyrotoxicosis was 300 mg. daily. Eight of these patients required a maintenance dose of 400 mg. or more daily.

No change was observed in the insulin requirement after thyroidectomy as compared with that of the controlled hyperthyroid state. When improvement did occur it was largely because the caloric requirement was decreased.

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CONGENITAL SYPHILIS IN MASSACHUSETTS

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PHYSICIANS are in agreement that congenital syphilis is preventable. Modern medicine has provided the medical profession with epidemiologic, diagnostic and therapeutic weapons so that congenital syphilis need not occur. Hence, the key to the solution of the problem of congenital syphilis is the prevention and control of syphilis in pregnancy.

Today, penicillin offers the most effective antibiotic yet discovered for the treatment of syphilis. It is the drug of choice in syphilotherapy because of its ease of administration, its safety and the brief period of time required to complete treatment. Its efficacy is equal if not superior to that of long-term treatment with arsenic and bismuth. In syphilis in pregnancy, results of treatment, as measured by the prevention of congenital syphilis, approach perfection; therefore, it is not for lack of an effective therapeutic agent that congenital syphilis occurs.

Massachusetts has a low reported syphilis rate. In the calendar year 1950, the syphilis rate based on reported cases was 28.1 per 100,000 population; the total venereal-disease rate was 80.1 per 100,000 population for the same period. This rate is low by comparison with the national syphilis rate for the fiscal year 1950 of 155.1[1, 2] per 100,000 population — more than Massachusetts' total venereal-disease rate. The lower rate in Massachusetts should mean that fewer pregnant women would be infected with syphilis and consequently fewer babies would be exposed in utero to *Spirocheta pallida*.

Figure 1 shows the reported cases of syphilis by stage of disease from 1938 to 1950 inclusive. Several observations can be made from it. First of all, the number of reported cases of syphilis was declining prior and subsequent to World War II; the latter decline began in 1947. However, with the military and industrial mobilization of World War II, the number of syphilis cases increased approximately 25 per cent — a lesson to be remembered during the present crisis. A second observation is how few cases of syphilis are discovered and reported during the primary and secondary stages. For example, in 1949 only 21.4 per cent of all cases of acquired syphilis were reported in the primary or secondary stages; in 1950 only 16.6 per cent were reported. How can syphilis be controlled when for every case of manifest syphilis reported 5 other patients are known to have been missed during their most infectious stages?

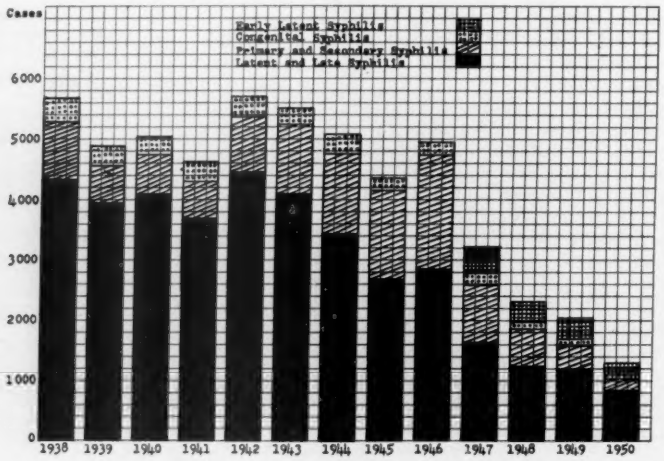

FIGURE 1. *Reported Cases of Syphilis by Stages in Massachusetts.*

Figure 2 illustrates the reported cases of congenital syphilis and congenital syphilis under one year of age. In 1949, 95.1 per cent were reported as over-

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one year, whereas in 1950, 97.3 per cent were reported. A shockingly large percentage of cases of congenital syphilis are not detected or reported during the first year of life.

Two laws have been passed to control congenital syphilis. The first is the law that requires both partners in an intended marriage to be examined and tested for syphilis by their physician before the wedding. Its object is to discover syphilis and to place an infected person under treatment before the infection can be communicated to an innocent partner. This law, as amended in 1950, requires that a party to an intended marriage infected with communicable syphilis be adequately treated before the physician may sign the premarital medical certificate, without which a marriage license cannot be issued. This provision is reasonable,[3] and with the use of penicillin no embarrassing delays to the wedding plans are necessary.

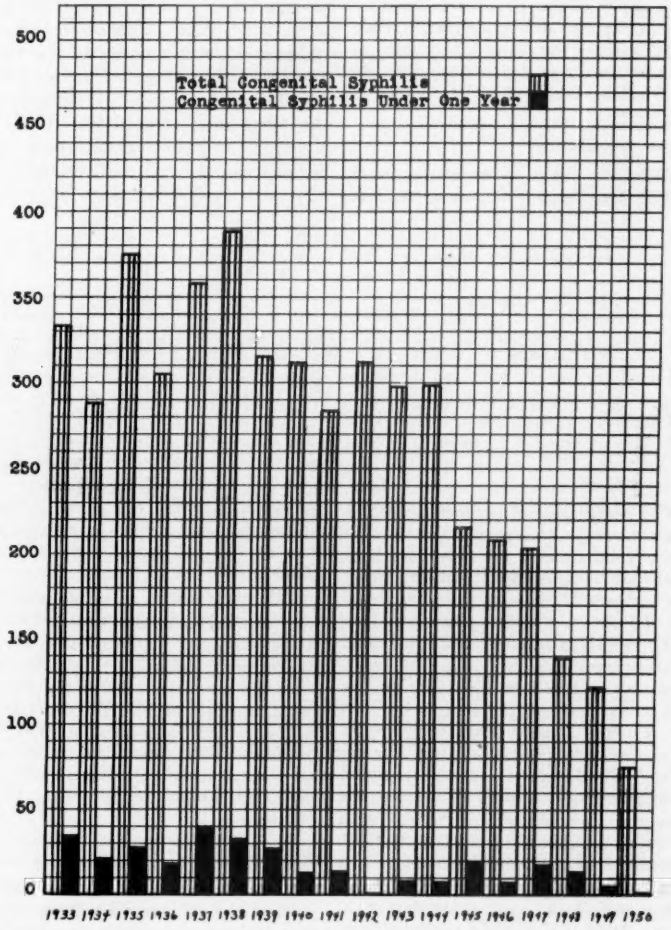

FIGURE 2. *Total Cases of Congenital Syphilis and Cases of Congenital Syphilis Under One Year of Age Reported in Massachusetts, 1933-1950.*

The prenatal-examination law of 1939 requires a physician attending a pregnant woman to take a blood test for syphilis at the first examination

(General Laws, Chapter 111, Section 121A). The earlier the diagnosis is made and treatment instituted, the better the prognosis for both mother and child.

In view of the availability and efficacy of penicillin, the low syphilis rate in Massachusetts and the premarital and prenatal examination laws, why does congenital syphilis continue to occur in Massachusetts? The object of this paper is to consider why these tragedies appear and to suggest possible remedies. To this end, the cases of congenital syphilis under one year reported to the Department of Public Health from 1946 to 1950 inclusive were studied.*

Age, Race and Sex Distribution

In Figure 2 are shown the total reported cases of congenital syphilis and those listed as under one year of age. The list of cases of congenital syphilis under one year shown in this graph does not indicate that these children were the only ones born with congenital syphilis during that year but rather that they were the ones whose cases were discovered and reported. To obtain a better picture of how many children were actually born, discovered and reported with congenital syphilis for a given year, cases of congenital syphilis over one year of age were allocated on the basis of the year of birth to those already reported in that year as under one year. Thus for the purpose of this study, for example, children with congenital syphilis reported in 1950 as being four years old were allocated to the year 1946, the year in which they were born with congenital syphilis. Accordingly from 1946 to 1950, inclusive, a total of 59 cases are included in this study. Of the 59 infants and children 31 (52.5 per cent) were boys and 28 (47.5 per cent) were girls. Analysis by race shows that 49 (83.0 per cent) were white, 9 (15.3 per cent) were Negroes and 1 (1.7 per cent) was Chinese.

The sex distribution by race shows that out of 49 white children, 24 (49.0 per cent) were boys and 25 (51.0 per cent) girls. Of the 9 Negro children 6 (66.7 per cent) were boys and 3 (33.3 per cent) girls. The one Chinese child was a boy.

*A state law requiring the destruction of old venereal-disease records after two years was repealed in 1948.

Marital Status

Is congenital syphilis more likely to be found in a single or a married mother? Table 1 shows that 50 (84.7 per cent) of the mothers were married, 7 (11.9 per cent) single, 1 divorced and 1 separated. Listing of marital status by race did not alter significantly the preceding data. However, it must be noted that 11.9 per cent of the women in this series were single. Estimates from the Division of Maternal Health are that 2 to 3 per cent, but no more than 5 per cent, of the women delivered in Massachusetts are single. This opinion is based on the illegitimacy reports for 1947 from Maine, Vermont and Rhode Island, where 3.5 per cent, 3.1 per cent and 2.3 per cent, respectively, of all live births in these states were illegitimate. If these opinions are valid, the physician must be doubly on the alert at the delivery of single women.

TABLE 1. *Marital Status and Race of Mother and Place of Birth in Cases of Congenital Syphilis Under One Year of Age in Massachusetts, 1946–1950.*

Marital Status	Total Births				Births in Hospitals				Births in Homes				Births in Other places			
	Total	White	Negro	Other races	Total	White	Negro	Other races	Total	White	Negro	Other races	Total	White	Negro	Other races
Single	7	5	2	—	6	4	2	—	1	1	—	—	—	—	—	—
Married	50	43	6	1	43	37	5	1	5	4	1	—	2	2	—	—
Widowed	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Divorced	1	—	1	—	—	—	—	—	1	—	1	—	—	—	—	—
Separated	1	1	—	—	—	—	—	—	1	1	—	—	—	—	—	—
Totals	59	49	9	1	49	41	7	1	8	6	2	—	2	2	—	—

Place of Delivery

Table 1 shows that 49 mothers (83.0 per cent) had hospital deliveries and 8 (13.6 per cent) had home deliveries. These ratios of hospital and home deliveries are essentially the same regardless of the race and marital status of the mother. However, in Massachusetts, 98.1 per cent (1948 data) of all deliveries occur in a hospital. This means that the physician may expect to see congenital syphilis at a hospital delivery but should be more keenly aware of possible syphilis when the child is born at home.

Prenatal Care

The criterion of prenatal care used in this study is that the mother visited her physician once or more during the period of gestation, although one visit to the physician during pregnancy cannot be considered adequate prenatal care; two visits is better but still hardly sufficient. Generally speaking, prenatal care would be adequate if the woman's visits to the physician were frequent enough to satisfy the doctor that the pregnancy was progressing satisfactorily and that the complications of pregnancy were prevented or discovered early and

treated adequately. Thus the number of visits would depend on whether there were complications, potential complications or normal progress. Normally, this would mean that the woman would visit her physician once a month after the diagnosis of pregnancy was made until the sixth month, twice a month during the seventh and eighth months and once a week during the ninth month. However, been adequate if a minimum of 2,400,000 units of penicillin, or 20 arsenicals and accompanying heavy metal had been given.

Although one can understand why 12 mothers with positive blood tests had congenitally syphilitic babies because they failed to return for treatment after the first visit (and, too, the failure of 10 others can be attributed to the fact that they had in-

TABLE 2. *Prenatal Care by Race and Marital Status of Mother in Cases of Congenital Syphilis Under One Year of Age in Massachusetts, 1946–1950.*

MARITAL STATUS	TOTAL				PRENATAL CARE				NO PRENATAL CARE			
	TOTAL	WHITE	NEGRO	OTHER RACES	TOTAL	WHITE	NEGRO	OTHER RACES	TOTAL	WHITE	NEGRO	OTHER RACES
Single	7	5	2	—	3	1	2	—	4	4	—	—
Married	50	43	6	1	38	31	6	1	12	12	—	—
Widowed	—	—	—	—	—	—	—	—	—	—	—	—
Divorced	1	—	1	—	—	—	—	—	1	—	1	—
Separated	1	1	—	—	—	—	—	—	1	1	—	—
Totals	59	49	9	1	41	32	8	1	18	17	1	—

for the purposes of this study only, two or more visits to a physician during pregnancy were considered adequate prenatal care for a mother with a negative blood test for syphilis. Accordingly, therefore, 41 women (69.5 per cent) had prenatal care, making one or more visits to the doctor, and 18 (30.5 per cent) had no prenatal care (Table 2). The majority of the married women had prenatal care (76.0 per cent), whereas more than half of the single women did not (57.1 per cent). Prenatal care or the lack of it had no relation to place of delivery. Of the 49 cases delivered in hospitals 35 (71.4 per cent) had prenatal care, whereas 14 out of a total of 18 with no prenatal care also had hospital delivery.

Of the 41 women who had some sort of prenatal care, only 18 were considered to have had adequate prenatal care according to our criterion. Of these, 14 were delivered in a hospital.

Most of these women sought prenatal care during the last trimester of pregnancy (48.9 per cent) (Table 3); the visits during the first and second trimester were about equally divided.

Prenatal Blood Test

Of the 41 women who had prenatal care 29 (70.7 per cent) had a positive Hinton test, 9 (22.0 per cent) had negative blood tests and 3 (7.3 per cent) had no blood tests at all.

Positive blood test. Examination of the records shows that of the 29 patients with positive blood tests 17 (58.6 per cent) received some sort of treatment and 12 (41.4 per cent) received none. They did not return to the physician after their first visit. Of the 17 who did receive some treatment, 10 (58.8 per cent) were inadequately treated, having failed to return to the physician to complete their course of treatment. Treatment was considered to have adequate treatment), why did 7 mothers who had proper treatment give birth to infected babies?

The analysis of the case histories of these mothers is revealing. One patient was considered to have had adequate treatment prior to this pregnancy, and because of a history of considerable treatment,—almost overtreatment (which was verified by the physician), — it was believed that there was no need of retreatment, even though the patient had a positive blood test at her first prenatal visit at the

TABLE 3. *Results of Blood Test on Mothers Having Prenatal Care.*

MONTH IN PREGNANCY AT TIME OF BLOOD TEST	TOTAL	POSITIVE	NEGATIVE	NO TEST TAKEN
1	3	2	1	—
2	2	1	1	—
3	5	3	1	1
4	1	—	1	—
5	5	5	—	—
6	5	3	1	1
7	4	2	2	—
8	7	5	2	—
9	9	8	—	1
Totals	41	29	9	3

eighth month. The mother was separated from her husband, and at the time of her original infection she had secondary syphilis, naming as her contact a man who on examination proved to have primary syphilis. She denied other contacts, although it is obvious that she must have had at least one other contact. The patient with primary syphilis was also named as the father of this baby; hence their sexual relations must have continued after treatment. Whether the mother also continued her relations with the unnamed and unknown contact of her original infection (or with others) could not be determined. The alleged father, on the basis of a

serologic test that was still positive without a significant rise in titer, was retreated after the delivery. Therefore, congenital syphilis may be accounted for in this case by reinfection or relapse.

Six cases were adequately treated during pregnancy. Two patients reported for prenatal care at the ninth month of gestation and after the report of the positive blood test were immediately started on treatment. However, in both cases treatment was completed just before labor, a minimum of 2,400,000 units having been administered. The failure in these 2 cases may be accounted for, therefore, by delay in treatment.

Another patient was treated for primary syphilis at the second month of pregnancy. Her husband, examined at the same time, had secondary syphilis. Although both husband and wife denied extramarital relations after treatment, it is problematical whether congenital syphilis in this instance can be accounted for by reinfection or relapse.

There remain 3 other cases in which the mother had received adequate treatment. In these 3 cases it was thought that there were inadequate grounds for a diagnosis of congenital syphilis. In one case, the infant of an adequately treated mother was reported to have congenital syphilis on the basis of the history of disease in the mother and the fact that the child failed to nurse properly, lost weight and became cachectic. No blood tests for syphilis were made on the infant because of difficulty in entering the baby's veins. There were no other signs or symptoms of congenital syphilis. A complete course of treatment with penicillin was given the child. A subsequent examination at one of the State Cooperating Venereal Disease Clinics revealed a negative blood test for syphilis, negative x-ray films and other signs of congenital syphilis. In 1 of the 2 remaining cases a diagnosis of congenital syphilis was made on the basis of a doubtful Hinton test in the child of an adequately treated mother. In the last case a baby born with hepatosplenomegaly and exfoliative dermatitis died ten hours after delivery. At post-mortem examination the blood Hinton test was negative, and there were no post-mortem signs of congenital syphilis.

Negative prenatal blood tests. Four mothers had negative prenatal blood tests, but after delivery the serum tests were positive. In each case the husbands were found to have early latent syphilis. Thus the failures in these 4 cases were attributable to an infection of the mother subsequent to the initial prenatal blood test.

The fifth patient had a negative prenatal blood test at the fourth month and as in the previous 4 cases the serologic test was positive after delivery. The husband was examined repeatedly but had no positive serum tests. The mother denied extramarital relations. Failure may then be accounted for by an infection subsequent to the first prenatal blood test, the source of which could not be established.

The sixth case followed to some extent the pattern of the fifth case. The mother had a negative blood test at the second month of pregnancy. Immediately after delivery she developed a dark-field positive eruption and had a positive serologic test. The husband admitted extramarital exposures and was found to be infected, as was his contact also.

In the seventh case both mother and father had a prior history of syphilis with adequate treatment and negative serologic tests. At the third month of pregnancy the mother's prenatal blood test was negative. Immediately after delivery it was found to be positive. The husband, examined while the wife was still hospitalized, had a dark-field positive eruption with positive blood tests. He admitted extramarital relations, and his contact was found to be infected. Therefore, reinfection accounted for this tragic failure.

The pattern of the eighth case was similar to the seventh, in that there was a prior history of adequately treated syphilis, negative serum tests, a negative prenatal blood test and positive serologic tests for both mother and father after delivery. However, both denied extramarital relations. Failure in this case could be due to reinfection subsequent to the initial prenatal blood test, although the possibility of relapse cannot be eliminated.

The last patient in this series of 9 had a prior history of adequately treated syphilis with negative serologic tests. A prenatal blood test was negative. During the first week post partum the serum tests were positive in undiluted serum on three occasions but negative in serial dilutions. The infant's blood was doubtful, and on this basis treatment was started immediately. No other signs of congenital syphilis appeared, and the validity of this diagnosis seems extremely doubtful.

Thus, in this group of 9 mothers with negative prenatal blood tests, the delivery of a baby with congenital syphilis can be attributed in at least 7 mothers to a syphilitic infection during pregnancy developing after the first prenatal visit. In another mother reinfection may be the cause for the unfortunate outcome, and in the ninth case the validity of the diagnosis of congenital syphilis is in doubt.

No prenatal blood test taken. Three mothers visited their physicians more or less regularly during this pregnancy. In no instance were less than two visits made, and although the physician had made urinalyses, hemoglobin determinations and pelvic measurements, in addition to the history and physical examination, at no time during the pregnancy was the blood tested for syphilis. The result of this omission was tragic. The State law concerning prenatal blood tests for syphilis is brief

and simple, and is found in Chapter 111, Section 121A, of the General Laws.

> Every physician attending a pregnant woman in Massachusetts during gestation shall, in the case of each woman so attended, take or cause to be taken a sample of blood of such woman at the time of first examination, and shall submit such sample for a standard serological test for syphilis to a laboratory of the state department of public health or to a laboratory approved for this test by the department; provided, that not more than one physician attending such a pregnant woman during gestation shall be required to take or cause to be taken such a sample.

Why did these physicians neglect to take a blood test? In one case, because the patient "looked nervous and embarrassed" after a pelvic examination including pelvimetry, the doctor decided to take the blood for a Hinton test at the next visit but forgot to do so.

The second physician responded to an emergency call after examining the patient and, like the first physician, forgot to take a blood test at her next visit.

The third physician simply forgot to take the blood sample until the birth of the syphilitic baby brought sharply into focus the cost of his forgetfulness.

To the physician practicing obstetrics, the lesson of these three cases is obvious.

Summary

This article analyzes 59 cases of congenital syphilis in children born during the period 1946 through 1950 in order to determine reasons for the persistence of the condition in Massachusetts and to suggest control measures.

These children were about equally divided as far as sex is concerned. Numerically there were more white than Negro infants, but the number of Negro children born with congenital syphilis was higher than expected on the basis of white and Negro population distributions in the State.

Approximately 85 per cent of the mothers were married. About 12 per cent were single; this percentage of single mothers is probably higher than expectancy for the general population of Massachusetts.

Again, 13.6 per cent of the mothers with syphilitic children were delivered at home, in contrast to the less than 2 per cent of home deliveries for this period of time for mothers in the general population.

Congenital syphilis occurred because of the following factors:

Ignorance and carelessness of the mothers in not seeking prenatal care was responsible in 30 per cent of the cases.

Approximately 20 per cent of the mothers with prenatal syphilis received no treatment at all because they failed to return to the doctor's office. Approximately half the mothers who did have prenatal care (adequate or inadequate) made their first appearance at the doctor's office during the last trimester.

Inadequate treatment of the mother accounted for an additional 17 per cent of this series of infected babies. Failure of the mother to return regularly to the physician for completion of scheduled treatment was the reason for the inadequacy of treatment.

Infection of the mother subsequent to the initial negative blood test was the cause of congenital syphilis in an additional 12 per cent of the cases.

Relapse or more probably reinfection was the cause of congenital syphilis in another 5 per cent.

Treatment failure appeared as the reason for congenital syphilis in 3 per cent of these cases. However, treatment was given late in pregnancy, and the completion of treatment coincided with the onset of labor.

Inadequate basis for diagnosis of congenital syphilis was believed to account for about 7 per cent of the cases reported.

Failure on the part of the physician to take a blood test for syphilis was the reason for congenital syphilis in the remaining 5 per cent of this series.

Recommendations

Although this series of cases is small it is clear where remedial measures are needed. The following recommendations are therefore offered:

A blood test for syphilis should be performed on all new patients in a physician's office, a clinic or a hospital.

Women adequately treated for syphilis and seronegative should have blood tests at least once in the first and second trimesters of pregnancy and monthly during the last trimester. At least two blood tests for syphilis, — one early and the other late in pregnancy, — should be made on all women known to have been sexually promiscuous; women having a history of any venereal disease; and single, divorced or separated pregnant women.

Women who have been adequately treated for syphilis but are still seropositive should be retreated with penicillin during each succeeding pregnancy.

Physicians and health workers must redouble their educational efforts to persuade mothers and potential mothers to seek early, adequate prenatal care.

Patients with positive prenatal serologic tests who neglect to return to the clinic or to the physician's office for diagnostic study and treatment should be referred to the Massachusetts Department of Public Health, Division of Venereal Diseases, for follow-up study if the physician or clinic workers have been unable to persuade them to return.

All patients infected with syphilis and the other venereal diseases should be questioned about contacts.

Hospital authorities admitting a patient in labor as a house-service case are required to take a blood test for syphilis unless they are satisfied that one has been taken during this pregnancy.

All cases of venereal disease should be reported by the physician — either with or without the patient's name. In either event, the information given is safeguarded by State law.

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AEROBIC ACTINOMYCES SEPTICEMIA*

Report of a Case

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ALTHOUGH actinomycotic infection can no longer be considered a rare disease, positive blood cultures with this group of organisms during life have been distinctly unusual. This is true despite the fact that blood-stream dissemination of the infecting organism is not uncommon, as shown by the relatively numerous cases of actinomycosis with widespread metastatic lesions reported in the literature. In his monograph Cope[1] makes no reference to the isolation of the organism from blood cultures. In several reported cases of generalized actinomycosis blood cultures were taken, but with the exception of the five cases noted below, no growth occurred.

The first case in which a blood culture positive for actinomyces was found was reported in 1932 by Freed and Light.[2] Their patient showed signs of widespread invasion, and four ante-mortem blood cultures positive for "actinomyces" and negative for bacteria were obtained.

Basu[3] reported studies on a strain of actinomyces obtained by blood culture from a fatal case of Ghosh[4] characterized by high fever and patches of bronchopneumonia.

Carrion[5] described a case of a thirteen-year-old boy with a febrile illness who had multiple abscesses and osteomyelitis of the left hip and left humerus. Two positive blood cultures were obtained, and pus from a draining inguinal gland showed *A. bovis*.

Uhr[6] reported a case of subacute bacterial endocarditis with fatal termination in a twenty-four-year-old man. Four blood cultures grew pure strains of *A. bovis*.

The only case of septicemia due to *Nocardia asteroides*, an aerobic actinomycete, was reported by Kirby and McNaught[7] in 1946. Late in the course of the disease the fungus was isolated from the sputum, the subcutaneous abscesses that developed and the blood.

The highly fatal nature of infection by aerobic actinomyces was emphasized by these authors in their review. Cecil[8] stated in 1940 that "all patients with pulmonary streptothricosis (nocardiosis) diagnosed by demonstration of the organism have died." Benbow, Smith and Grimson,[9] however, recently reported apparent arrest of *N. asteroides* infection in two cases in which sulfonamides, potassium iodide and x-ray therapy were used. In both instances pulmonary infiltrations as well as subcutaneous abscesses were present.

Because proved cases of actinomycotic septicemia, — particularly those caused by aerobic strains, — are extremely rare and are almost uniformly fatal, a case in which complete recovery apparently followed the use of the newer antibiotics is presented below.

CASE REPORT

R. S., a 50-year-old man, was admitted to the Mt. Sinai Hospital on March 6, 1950, because of chills and fever. He had been in good health until about 1 month previously, when he first noted the onset of anorexia, weakness and easy fatigability. Two weeks prior to admission he developed a sudden shaking chill, followed by high fever and profuse perspiration. He also complained of soreness of the mouth, tongue and throat. Although he continued to work he had irregular periods of nocturnal chills and fever, and his anorexia and weakness increased.

On admission he appeared acutely ill. The temperature was 104.6°F., the pulse 90, the respirations 20 and the blood pressure 130/80. The tongue was beefy red and dry, and the pharynx was only moderately injected. There was no lymphadenopathy. A few moist rales were heard in the right paravertebral region near the base, and a small area of percussion dullness was noted in this location. A soft systolic murmur was heard at the apex. The liver edge was barely palpable beneath the right costal margin and was nontender. The spleen was not palpable. Neurologic examination was essentially normal and the remainder of the physical examination was unremarkable.

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Selected pertinent laboratory data are listed in Tables 1 and 2. On admission the only significant laboratory findings consisted of a mild anemia and leukocytosis. Agglutination tests against typhoid, paratyphoid A and B, brucella and *B. tularense* were all negative. A spinal-fluid tap revealed normal findings. The electrocardiogram was within normal limits. A roentgenogram of the chest showed a small area of infiltration in the right paravertebral region (Fig. 1).

On the first hospital day no specific therapy was administered, and daily blood cultures were ordered. Because of the patient's obviously desperate condition, together with the finding of a definite leukocytosis, treatment with crystalline penicillin, 1,200,000 units daily, was initiated on the second hospital day. The patient's condition grew steadily worse, however, the temperature rising to 104°F. daily. On the fifth hospital day the first blood culture obtained was found to be positive for a non-acid-fast, branching, filamentous gram-positive organism that was tentatively classified as one of the actinomycetes. An identical organism was subsequently obtained from the blood cultures taken on the second and third hospital days. The following treatment schedule was accordingly instituted on March 10: penicillin, 10,000,000 units intravenously in 1000 cc. of normal saline solution by slow drip daily, 500,000 units of penicillin every 3 hours intramuscularly, streptomycin, 0.5 gm. every 6 hours intramuscularly, sulfadiazine, 2.0 gm. every 4 hours, and sodium iodide, 1 gm. intravenously (added to the intravenous infusion).

Within 24 hours after the start of this intensive therapy the temperature began to fall, reaching normal on March 12. There was a corresponding fall in the white-cell count to 8650. However, on March 13 the patient began to complain of generalized pruritus, which was associated with an erythematous morbilliform eruption involving the trunk and upper and lower extremities. With the appearance of the exanthem the temperature again began to rise and by March 15 had reached 104°F. The skin eruption and the temperature rise were interpreted as evidence of drug toxicity; accordingly, all drugs except penicillin were discontinued. The dosage of penicillin was at this time increased to 20,000,000 units daily (intravenously) and maintained at 4,000,000 units (intramuscularly). By this time in-vitro drug-sensitivity studies had been completed (Table 3), and it was determined that the organism cultured from the blood was very sensitive to aureomycin, moderately sensitive to penicillin and not inhibited to any extent by either Chloromycetin or streptomycin. Consequently, the administration of aureomycin was begun in doses of 500 mg. every 3 hours by mouth and the penicillin was continued with dosage unchanged.

The patient's condition had by now deteriorated to an alarming degree. His respirations became very rapid and shallow, the respiratory rate rising to 50 per minute, and he was cyanotic. He complained of severe substernal and right-chest pain. Auscultation of the lungs revealed moist rales, wheezes and rhonchi throughout both lungs. The patient was placed in an oxygen tent at this time, with subsequent diminution of the cyanosis. Soon after the addition of the aureomycin to the treatment schedule the temperature again began to fall; after five days it became stable at approximately 99°F. rectally. The aureomycin, however, caused nausea, vomiting and diarrhea; accordingly, parenteral administration of the antibiotic was begun, in a dosage of 2.8 gm. daily.

The rectal temperature remained below 100°F. for six days, during which period clinical improvement again took

TABLE 1. *Selected Routine Laboratory Studies.*

DATE	RED-CELL COUNT	HEMOGLOBIN	WHITE-CELL COUNT	URINE ALBUMIN	NONPROTEIN NITROGEN	BLOOD SUGAR
	x10⁶	%			*mg./100 cc.*	*mg./100 cc.*
March 7	3.92	78	21,500	0	36	130
March 13	4.45	81	8,650	4+	26	101
March 22	3.90	75	20,550	tr.	47	
April 2	3.23	52	9,750	4+	52	114
April 25	3.83	65	8,050	1+	55	112
August 7	5.20	103	11,350	0	43	

TABLE 2. *Liver-Function Studies.*

DATE	ICTERIC INDEX	TOTAL PROTEIN	ALBUMIN	GLOBULIN	VAN DEN BERG TEST		CHOLESTEROL	ESTERS	CEPHALIN FLOCCULATION	THYMOL TURBIDITY	BROMSULFALEIN RETENTION
					1′	15′					
		gm.	*gm.*		*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*			%
March 9									2+		
March 10		7.4	3.6	3.8	0.46	0.7	103	48			
March 25	22	6.3	0.9	5.4	4.1	5.9	130	26			
March 27	36	6.3	1.3	5.0							
March 30	38	6.5	1.8	4.7							
April 1									2+		
April 3	19	6.7	1.7	5.0							
April 10	25	7.0	2.0	5.0							
April 13	14	8.0	1.9	6.1							
April 25	6	9.3	2.1	7.2							
May 2	5	9.5	3.1	6.4	0.2	0.2	136	88	4+	4.6	(5 min.) 40 (45 min.) 7
May 10		9.5	3.1	6.4							
May 18		9.6	4.0	5.6							
August 7	10.5	7.85	4.35	3.50			190		3+		

TABLE 3. *Antibiotic Sensitivities of Organism Isolated from Blood Culture of R.S.*

AGENT	SUSCEPTIBILITY RANGE	RELATIVE SUSCEPTIBILITY
	l cc.	
Penicillin	0.1 unit	Moderate
Streptomycin	>4–15 microgm.	Slight
Aureomycin	4 microgm.	Very
Terramycin	<4 microgm.*	Very
Chloromycetin	>10 microgm.	Resistant

*Zone of inhibition appreciably greater than that produced by aureomycin.

place. The skin eruption had also cleared by now, but on March 24 icterus was noted, and marked hypoalbuminemia and hyperglobulinemia developed. The patient's mental condition remained poor; he was confused and disoriented and occasionally semistuporous. Since he had remained essentially afebrile for 1 week, and because of the appearance of the jaundice and the persistence of the confused mental status, it was decided to stop all medication on March 27.

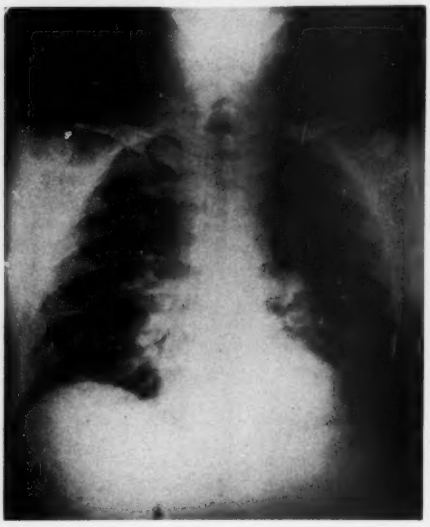

FIGURE 1. *X-Ray Film Taken March 17, 1950, Showing Enlargement of Right Hilus with Streaked and Mottled Infiltration Extending Outward from Hilus.*

This was done because the large doses of these antibiotics could not be ruled out as a contributory factor in the obvious hepatic derangement and cerebral involvement.

The patient remained essentially afebrile for 3 days after the discontinuance of therapy, but on March 30 he again complained of chest pain in the right lower axillary region, particularly on deep inspiration. Auscultation at this time revealed a loud pleural friction rub in this region. In addition, moist rales were heard at the left base. A chest film at this time showed a dense band extending across the midportion of the left lung with peritruncal mottling in the posterior portion of the left base, probably representing a pneumonic infiltration with a band of atelectasis. The right lung appeared relatively clear.

On the following day the temperature again began to rise, and penicillin and aureomycin therapy was resumed. On April 1, terramycin became available, and this drug was added to the other two antibiotics, the patient receiving 250 mg. every 2 hours. Within 24 hours after terramycin was started the temperature fell and reached normal on April 3. An in-vitro sensitivity test disclosed that the infecting organism was extremely sensitive to terramycin, significantly more so than to aureomycin. On April 10, aureomycin and penicillin were discontinued and from this time on the temperature fell and remained within normal limits for the remainder of the hospital stay.

The terramycin was finally stopped on April 23. Jaundice slowly subsided and the serum albumin rose to normal levels. Up to the time of discharge rales were heard intermittently at the left base, and the final chest x-ray film still showed an area of density in the posterior basal segment on the left, though much less marked than on previous films (Fig. 2). Frequent blood cultures were taken after the discontinuance of terramycin, all of which were sterile. The patient was discharged on his 76th hospital day to continue his convalescence at his home.

The patient was last seen on August 7, 1950, approximately 6 months after the onset of his illness. At this time he felt completely well and had regained his former weight and strength. He had remained afebrile, and no evidence of recrudescence of the infection was noted. Anemia was no longer present, and the serum-globulin value had returned to normal. The film of the chest still showed the small area of density in the left lower lobe. As all other findings seemed to indicate

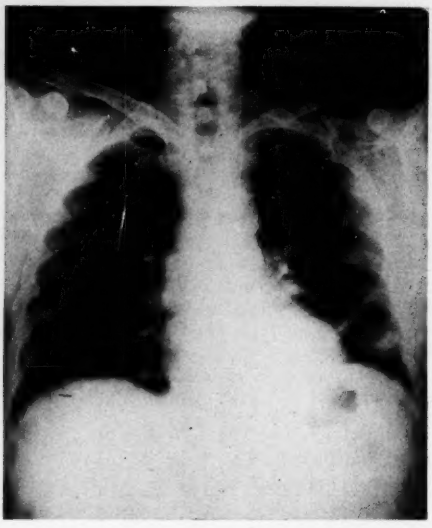

FIGURE 2. *X-Ray Film Taken May 13, 1950, Showing Small Area of Density in the Left Posterior Basal Segment. The right lung is clear.*

complete absence of actinomycotic infection, it was thought that this density represented scar tissue.

MICROBIOLOGIC STUDIES

The organism began to grow within forty-eight hours under aerobic conditions, somewhat more rapidly at 36°C. than at room temperature. The original cultures were odorless, but on subculture several developed a characteristic soil-like odor.

Growth on Solid Media

On subcultivation on the surface of blood agar plates the colonies were gray, hemolytic and somewhat elevated above the surface, usually with raised centers and radial striations but also with a smooth surface. On Czapek's synthetic medium there was far more rapid and abundant development of the

white, powdery top surface, extending over the entire surface of the colonies rather than limited to the center, as in the case of the richer media.

Microscopical Examination

The organisms were non-acid-fast, predominantly gram-positive nonfragmenting, branching, delicate filaments, of the order of one micron or less in cross-section. When the white, powdery surface layers were examined, they were found to contain large numbers of round to oval conidia, arising from hyphae in chains and in clusters whose mode of origin was not determined (Fig. 3). On ordinary smears, these conidia strongly resembled gram-positive cocci or short rods; serial observation of wet mounts and stained preparations of young cultures revealed that these bodies were conidia rather than contaminating micro-organisms.

Pathogenicity

The colonies from two agar slants were ground in a mortar and suspended in 5 ml. of sterile saline solution. One rabbit inoculated intravenously with 1 ml. of the suspension suffered no ill effects and showed no lesions when sacrificed in six weeks. Four mice were inoculated intraperitoneally with 0.5 ml. and remained entirely well. Three guinea pigs also inoculated intraperitoneally with 0.5 ml. also remained well.

Discussion

In addition to its rarity, this case presents several features of interest. The infrequency with which positive blood cultures have been reported from cases of human actinomycosis calls for an explanation, especially as generalized infection is not rare. In the majority of cases involving the anaerobic strains, inadequate technics of culture may be responsible. Possibly, too, the tendency of these organisms to form aggregates may make isolation from the bloodstream less certain. When, rarely, infection develops from aerobic actinomyces, these organisms are apt to be dismissed as the ubiquitous, soil-inhabiting contaminants that they are, especially when clinical suspicion is not aroused by sinus tracts, sulfur granules and so forth. In the case presented here, similar doubts were entertained. That the organism recovered from blood cultures was the offending pathogen is supported by the following considerations:

The isolation of the same organism from *3 successive blood cultures.*

The absence of contaminating aerobic actinomyces in the laboratory in the current material under study.

The clinical course.

The correlation of the effectiveness of antibiotic therapy, — especially penicillin, aureomycin and terramycin, — with the in-vitro sensitivity of the organisms and the apparent effectiveness in vivo as judged by the response of the patient.

The antibiotic drugs that were first utilized when the diagnosis of actinomycotic septicemia became evident had all been reported as effective in this type of infection, particularly in the anaerobic variety, alone or in combination.

Because of the extremely grave prognosis in this case, we decided to use in combination all the therapeutic agents that had previously appeared effective against actinomycotic infection. Furthermore, it was not considered reasonable to delay the institution of specific therapy until in-vitro antibiotic-sensitivity studies could be completed. Accordingly, treatment with sodium iodide, sulfadiazine, streptomycin and massive doses of penicillin (14,000,000 units daily) was begun. The initial response to this intensive therapy was gratifying, as evidenced by the relatively rapid fall in the temperature and white-cell count, as well as by the obvious improvement in the patient's clinical condition.

Figure 3. *Gram Stain Showing Branching Mycelia and Conidia (x700).*

At this time no report of the efficacy of aureomycin in the treatment of actinomycosis had as yet appeared in the literature. However, subsequent to our experience with aureomycin in this case,

McVay and his associates[10] reported a case of cervicofacial actinomycosis cured with aureomycin.

The second phase of treatment, consisting of massive doses of aureomycin and penicillin, again appeared to have brought the infection under control, but it was thought necessary to discontinue these drugs after eleven days because of the onset of cerebral and hepatic derangement, which was considered possibly due to the large dosage of the antibiotics. This led to the third and final phase of treatment, in which terramycin played the major role. Early in this phase penicillin and aureomycin were discontinued, and terramycin alone was utilized. In this connection it should be noted that relatively small oral doses of terramycin (3.0 gm. daily) were administered, yet the infection appeared to be completely arrested. This certainly would indicate the marked effectiveness of this new antibiotic agent in this type of actinomycotic infection.

Although the organism under study has many points of similarity to several of the 73 described species of the Streptomyces[11] it does not seem identical with any of them. The naming of a new species before more exhaustive study has been made is not suggested herewith; we have thus far identified it only as *Streptomyces sp.*

Summary

A case of septicemia due to an aerobic actinomycete, with primary involvement of the lungs, is reported.

Apparent arrest of the infection was achieved by means of combined treatment with the newer antibiotics, including terramycin, aureomycin and penicillin.

The microbiologic characteristics of the causative organism are described; these suggest that it should be included in the genus *Streptomyces*.

A review of the literature is presented, indicating the rarity of proved bloodstream infection by the actinomycetes. The reasons for the paucity of reports of positive blood cultures from cases of human actinomycosis are considered.

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"WETHERBEE AIL"*

The Inheritance of Progressive Muscular Atrophy as a Dominant Trait in Two New England Families

MADELAINE R. BROWN, M.D.†

BOSTON

PROGRESSIVE muscular atrophy has never been considered hereditary, although occasionally two members of a family have been reported as having the disease. During a study of the old records at the Massachusetts General Hospital of cases diagnosed as progressive muscular atrophy, two reports were found of patients who said that the disease had been present in several generations of their families.

CASE REPORTS

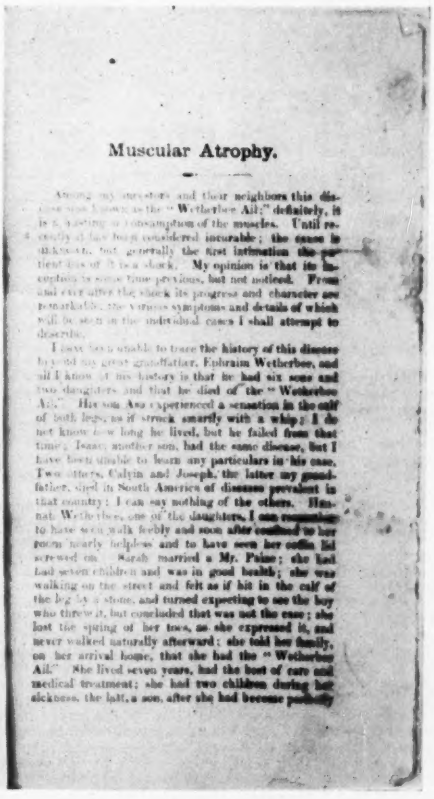
CASE 1. In 1872 a 40-year-old chairmaker from Gardner, Massachusetts, entered the Massachusetts General Hospital and was discharged with the diagnosis of progressive muscular atrophy. In 1874 a pamphlet entitled "Muscular Atrophy" written by himself was added to his record (Fig. 1). The history, in his own words, is as follows: "Among my ancestors and their neighbors this disease was known as the 'Wetherbee Ail'. . . I have been unable to trace the history of this disease beyond my great grandfather, and all I know of his history is that he had six sons and two daughters and that he died of muscular atrophy. His son Asa experienced a sensation in the calf of both legs, as if struck smartly with a whip; I do not know how long he lived, but he failed from that time; Isaac, another son, had the same disease. Two others, Calvin and Joseph, the latter my grandfather, died in South America of diseases prevalent in that country. Hannah, one of the daughters, I can remember to have seen walk feebly and soon after confined to her room nearly helpless, and to have seen her coffin lid screwed on. Sarah married, had seven children and was in good health; she was walking on the street and felt as if hit in the calf of the leg by a stone, and turned expecting to see the boy who threw it, but concluded that was not the case; she lost the spring of her toes, as she expressed it, and never walked naturally afterward; she told her family, on her arrival home, that she had muscular atrophy. She lived seven years and had two children during her sickness. She had eight living children, all of whom are in good health.‡

"I now come to the case of my father. When about thirty-nine he remarked that he was growing old fast and some of the neighbors discovered a slight limp in his walk. He first discovered a weakness in the right thumb, being unable to open his pocket knife in the usual way. The right hand and arm lost strength faster than the left; and contrarily, the left leg failed the fastest. The progress of the disease was rapid; he suffered somewhat from painful muscular contractions or cramps, otherwise he had but little pain. The larger muscles of the arms and legs became soft and flabby and diminished in size. He got about the house with crutches several months, comfortably. In the summer of 1846 he became nearly helpless. Mother and myself lifted him to his feet and to and from his bed and chair. So he wasted in flesh and strength and died on the 10th of October, 1846, a little more than two years after the onset."

A note on the record dated 1874, written by Dr. Benjamin Shaw, director of the hospital, states that a brother of the patient had recently complained of symptoms similar to those of the patient (Fig. 2).

"Late in '69 or early in '70, I noticed a fibrillous contraction just above the right knee, about half way from the anterior to the inside. It is a tremulous twitching of the muscles, which is seen in the muscles of slaughtered animals after the skin is taken off. It is painless but somewhat disagreeable and more noticeable after retiring. In two or three days it was gone. About the 20th or 25th of March '71 I noticed for the first time that I went up stairs with much difficulty, the trouble seeming to be in the right thigh.

"I was a little anxious about all this but did not suspect any permanent lameness existed. On May 11th, as I was



Muscular Atrophy.

Among my ancestors and their neighbors this disease was known as the "Wetherbee Ail;" definitely, it is a wasting or consumption of the muscles. Until recently it has been considered incurable; the cause is unknown, but generally the first intimation the patient has of it is a shock. My opinion is that its beginning is some time previous, but not noticed. From and ever after the shock its progress and character are remarkable, the various symptoms and details of which will be seen in the individual cases I shall attempt to describe.

I have been unable to trace the history of this disease beyond my great grandfather, Ephraim Wetherbee, and all I know of his history is that he had six sons and two daughters and that he died of the "Wetherbee Ail." His son Asa experienced a sensation in the calf of both legs, as if struck smartly with a whip; I do not know how long he lived, but he failed from that time; Isaac, another son, had the same disease, but I have been unable to learn any particulars in his case. Two others, Calvin and Joseph, the latter my grandfather, died in South America of diseases prevalent in that country; I can say nothing of the others. Hannah Wetherbee, one of the daughters, I can remember to have seen walk feebly and soon after confined to her room nearly helpless and to have seen her coffin lid screwed on. Sarah married a Mr. Paine; she had had seven children and was in good health; she was walking on the street and felt as if hit in the calf of the leg by a stone, and turned expecting to see the boy who threw it, but concluded that was not the case; she lost the spring of her toes, as she expressed it, and never walked naturally afterward; she told her family, on her arrival home, that she had the "Wetherbee Ail." She lived seven years, had the best of care and medical treatment; she had two children during her sickness, the last, a son, after she had become painfully

FIGURE 1.

going on an errand in the morning I stopped to throw a stone at a small hawk in an apple tree but fell myself and the hawk flew away. About this time I had severe cramps in the right thumb. I consulted a doctor about this time, and began a regular course of treatment. From May 11th to the first of June the tremulous twitching was very marked, and I had occasional painful cramps. I continued to lose

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‡This member of the family did not have progressive muscular atrophy, as two or three years is the average time of survival. None of her many children had the disease.

strength all summer and was obliged to give up some kinds of work.

"September 1st, I found that the right thigh measured only sixteen inches, while the left measured nineteen. I used a cane at this time and found it of much service. At this time I rode to and from the shop. About the first of November I found the left leg began to fail. The first of January, 1872, I found much difficulty in walking only a short distance. I gave up work and went to the Massachusetts General Hospital, for five weeks; but no effect of the treatment was apparent, think the right thigh had decreased to fourteen and one-half inches, in one year. There was but very little strength in the right leg, the muscle of the thigh was very flabby and the heat was lower than in the other leg. I resumed my occupation in February. The fibrillous contractions and painful cramps had by this time nearly ceased in the right leg but were visible in the left; also, noticed weakness

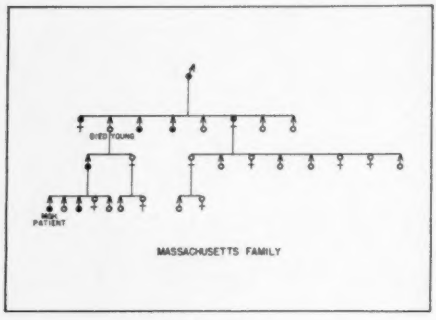

FIGURE 2.

in the right thumb, especially when cold, and could not hold a carpenter's pencil in the usual way. Late in May I could bear no weight on my left toes. Meantime I had bandaged my right foot and leg to the knee, on account of swelling.

"From this time the progress of the disease was marked and rapid, especially in the ball of the right thumb and the left thigh. I now found it unsafe to step without a cane, or out of reach of something permanent. I gave up walking in the shop, used a wheel-chair and was during the fall put into a buggy by a strong man. I continued to work through December, excepting some of the coldest days, but on the last afternoon of the year of '72, I fell and severely sprained the left knee; was obliged to quit work and have done nothing since.

"At no time, since I first felt the lameness in the right thigh, have I been able to say with truth, that I was a little better, or even about the same; but that I was not so strong as I was a month previous. This disease never stands still. I will close this sketch by saying that at this writing I cannot stand alone, have no control of the right leg whatever and cannot move the toes. The left is very weak; both feet, and the legs below the knee, are somewhat cold most of the time. I dress without assistance. My arms are not strong enough to raise my weight to my feet; have not strength to cough or sneeze with any force. Have a fair appetite and sleep well. It is probable that nearly every muscle in the system is affected, as I have felt the cramps and tremulous contractions in nearly every part. There is no loss of sensation in any part. The large muscles of the right thumb are much wasted, the whole hand has a bony appearance and the third finger droops. Sometimes I cannot pick up a pin, and my writing is scarcely legible. I gave up all treatment six months ago, as I could never see any difference in the progress of the disease, while under treatment and while not."

CASE 2. In 1905 a 36-year-old pipe-organ maker from Brattleboro, Vermont, entered the Massachusetts General Hospital and was told that he had progressive muscular atrophy. He stated that his father (at the age of 43), his grandfather and his father's brother had had paralysis of gradual onset that finally affected the muscles of the throat.

For 8 or 9 weeks before admission the patient had noticed a weakness of the right knee and a dull ache in the calf and knee. Later he had noticed weakness of the left knee and a twitching of the muscles of the legs and arms. Neurologic examination disclosed atrophy of the right thigh and both calves. Fibrillary twitchings were present in both thighs. Sensation was intact. Deep reflexes in the arms were intact. The right knee jerk was sluggish, the left lively. There was no clonus, and normal plantar responses were obtained. The abdominal and cremasteric reflexes were present.

In 1880 Dr. William Osler published a paper entitled "On Heredity in Progressive Muscular Atrophy as Illustrated by a Vermont Family."[1, 2] He had seen a member of the family in the Montreal General Hospital and discovered that 13 persons in 2 generations had had or died from the disease after the age of forty (Fig. 3). His patient was a forty-seven-year-old Vermont farmer who had complained of weakness of the left leg and twitching muscles over various parts of the body for fourteen months. The left leg was smaller than the right and two-

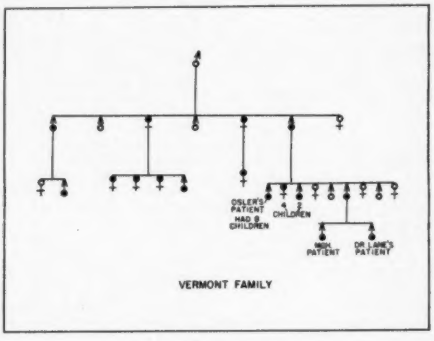

FIGURE 3.

point sensation in the legs was reduced. The electrocontraction was preserved.

The *Bibliotheca Osleriana* mentions that appended to the reprint of the case report in the Osler Library at McGill University Medical School are six letters to Osler concerning additional members of the family.[3] Dr. William Francis kindly sent me the letters; three, written in the 1890's, were from the son of Osler's patient, and three were from Dr. Winfred Lane of Brattleboro, Vermont. In 1912 Dr. Lane had written Osler that two brothers, nephews of Osler's patient, had had progressive muscular atrophy. The onset in both cases had occurred at the age of thirty-six; one brother was the patient described in Case 2, who had entered the Massachusetts General Hospital in 1905. The other was under the care of Dr. Lane. One letter, dated seven months later, was written by Dr. Lane, saying

that the disease had progressed and his patient had died. It has recently been ascertained that all three brothers of the patient admitted to the Massachusetts General Hospital died of progressive muscular atrophy. One sister did not have the disease.

Conclusions

There is little doubt that members of these two families had a progressive degeneration of the anterior horn cells of the spinal cord and that bulbar palsy was the cause of death in the Vermont family. Osler's article has been lost to the literature of progressive muscular atrophy because subsequent authors have believed that he was dealing with peroneal (Charcot–Marie–Tooth) atrophy.[4] Progressive muscular atrophy is an inherited abiatrophy of the motor nerve cells. In the two families described, the type of inheritance was that of a mendelian dominant for several generations.

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MEDICAL PROGRESS

DISEASES OF MUSCLES

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BOSTON

Myotonia

Myotonia Atrophica (*Dystrophia Myotonica*)

THE pathologic aspects of the atrophic form of myotonia, a chronic hereditary disease of muscle, characterized by the development of cataract with muscular and glandular dystrophy, have been considered by Farber,[1] who found striking changes in the lens in 3 cases. A slit-lamp examination revealed shiny flakes, white dots and dust-like opacities in a sharply defined layer under the anterior and posterior capsule. The flakes were green and blue, as found in cholesterol crystals. The same type of cataract, according to Farber, is seen in mongolism, traumatic myxedema, postoperative tetany and cretinism. Bertrand[2] reported on 5 patients with myotonia atrophica; each had megalocolon. Ferraris[3] found sclerodema, confirmed by biopsy, in 1 patient. Rinzler[4] observed a man, aged forty-two, with myotonia and an abnormal electrocardiogram showing left-bundle-branch block. The patient also showed a tolerance to atropine. DeWind and Jones[5] summarized the cardiovascular observations in the literature and added six observations of their own. Ninety-eight patients had had electrocardiograms; 61 of the tracings could be considered abnormal. The most frequent abnormalities were low P wave, prolonged PR interval, prolonged intraventricular conduction time and possible elevation of the ST segment. Although atropine caused mydriasis and dryness of the mouth in two patients it did not change the PR interval. These changes appeared to be unrelated to any significant cardiac, physical or roentgenographic findings, although unexplained cardiomegaly was not infrequent. Nor could these findings be attributed to coronary disease or to the quinine frequently administered to these patients. The heart muscle at autopsy has shown no deviation from the normal. The authors suggest the possibility that the myocardium itself may be involved in myotonia atrophica by the same process that affects the skeletal muscle. Ziesler and his associates[6] found that there was no increase of creatine in the urine in spite of the reduced muscle mass and normal kidney tubules.

Treatment. Shy, Brendler, Rubinovitch and McEachern[7] treated two patients with myotonia atrophica with cortisone. The myotonic response was abolished, but the patients were not otherwise affected.

General Considerations

The most complete book on myotonia published in recent years, written by Thomasen,[8] was published in Denmark in 1948, with an excellent English translation. During World War II, when Denmark was occupied by the Germans, the author visited every family in Denmark with known cases of myotonia atrophica or myotonia congenita (Thomsen's disease). In his book the historical background of both disorders is covered in full; many photographs of patients are included, and there is a bibliography of nearly 500 references.

Thomasen found myotonia atrophica spread over Europe, the Americas and Japan. It was far more frequent than Thomsen's disease. He studied 21 Danish families comprising 1148 members, 874 of whom were living. Among the living, 101 had certain myotonia atrophica; 17 had cataract only. The disease was inherited equally in males and females as a dominant trait. Mental deficiency and reduced working ability frequently resulted in social deterioration. Fertility was reduced; a high

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proportion of the patients were unmarried. Cataract was found as a solitary symptom in parents. Lenticular opacities occurred in 87 per cent of the patients seen. Cataracts rarely became mature before the age of forty-five. Frontoparietal baldness was found in 83 per cent of the males and in 20 per cent of the females.

Muscle weakness affected the facial movements, mastication and the use of the tongue, neck and forearms. Myotonia was most often localized in the finger flexors. There were no characteristic changes in the creatine-creatinine excretion in the urine of the 3 patients studied.

Gonadal dystrophy was found in 86 per cent of the males and presumably in 64 per cent of the females, who had menstrual disturbances. The majority showed decreased excretion of testicular hormone and estrin and reduced libido and sexual potency. Lowered basal metabolism, without myxedematous symptoms, was found in many patients. Most often the thyroid gland showed colloidal changes. There were no definite changes in the internal secretion of the pancreas, although the blood-sugar level was often a little low. There is no special clinical basis for the postulation of atrophy of the cortex of the suprarenal glands. Attempts at substitution therapy resulted in subjective improvement in only 3 cases. The functioning of the parathyroid glands was seemingly normal.

Frontal hyperostosis occurred in 83 per cent of males and 16 per cent of females. Acrocyanosis and vasospasm was present in two thirds of the patients and in 3 out of 12 who had abnormal electrocardiograms, with prolongation of the conduction time. The hearts of 3 other patients were examined at autopsy; no gross or microscopical pathologic changes were found in the myocardium.

Thomasen found that quinine reduced the myotonia but that there was rarely sufficient indication for this treatment. No efficient treatment of dystrophica myotonia is known.

Myotonia Congenita (Thomsen's Disease)

Thomasen[8] also reported on five families in Denmark with Thomsen's disease, including that of Dr. Asmus Julius Thomas Thomsen, who had the disease himself. This muscular disease is characterized by a prolongation of muscular contraction, with frequent hypertrophy of the particular muscles involved. In two of the five families investigated the inheritance was of the dominant type; in two the disease was found in siblings but not in the parents. The Thomsen family history of the disease dates back to 1742. Dr. Thomsen's original paper was published in 1876. None of the patients had ocular, cardiac, endocrine or mental changes. In contrast to patients with myotonia atrophica, all patients with Thomsen's disease were able to support themselves financially. Electromyographic records disclose intermittent "showers" of potential oscillations lasting a few seconds. These occur during periods of non-activation of the affected muscles.

Treatment. According to Thomasen, most of the patients with Thomsen's disease learn how to reduce the hampering of their movements by keeping in constant activity. Two patients, with severe general myotonia, tried quinine treatment but did not wish to continue, although the treatment had a beneficial effect. Two other patients were treated with 1.5 to 1.75 gm. of quinine per day. The hampering of their movements did not completely disappear but was considerably reduced. Thomasen found that there was clear habituation to the use of quinine, rendering the drug ineffective after about eight days' constant administration. Therefore eight-day intervals were allowed between the eight-day periods of treatment. Remarkably few inconveniences were suffered by the patients from large doses of quinine. He found that calcium ions given orally in large doses accentuated the effect of the quinine.

Siirala[9] reported in 1949 on an extensive clinical and pharmacologic study of myotonia congenita as observed in Finland. Eight cases were observed. Unusual features noted were the late onset of stiffness in the tongue and facial muscles, pain as a material symptom, sensory symptoms in the lower extremities (symmetrical and reversible), hyperhidrosis and respiratory arrhythmia. Sodium, potassium, calcium and magnesium values in muscle tissue were found to be normal. Siirala also noted that the myotonic contraction is reversible in that it can be abolished by voluntary movements repeated in immediate succession. "Percussion myotonia" was almost abolished by repeated tappings. The myotonia in Thomsen's disease may not be identical with the contractions seen in myotonia atrophica.

Muscular Dystrophy

Tyler and Stephens,[10] using the complete genealogical records of the Church of Jesus Christ of Latter Day Saints, Utah, took advantage of an unusual opportunity to study the heredity of muscular dystrophy. A dystrophic man, born in England in 1775, migrated to Utah and had dystrophic children by three wives. There were 1249 descendants in this one family; 159 are known to have facioscapulohumeral muscular dystrophy. The authors examined 240 members of the family and found that 58 living members had dystrophy. The onset of symptoms occurred between the ages of seven and twenty. Heredity was Mendelian dominant. There were no breaks in the line of dystrophic persons, and no unaffected member had ever had a dystrophic child. No other hereditary traits were detected.

Boyes and associates[11] were able to study a dystrophic family in both Canada and England. Thirteen members in 3 generations were found to have

facioscapulohumeral dystrophy. All appeared to lead relatively normal lives. A simple dominant mode of transmission was indicated. Brown[12] found records of 71 patients with muscular dystrophy admitted to the Massachusetts General Hospital from 1870 through 1947. Fourteen persons had siblings with muscular dystrophy. In no case was evidence found of an affected parent or child. The inheritance of all types of muscular dystrophy in this series, including the facioscapulohumeral, was recessive.

Azzi[13] described atrophy of the tongue in a case of progressive muscular dystrophy. An unusual example of dystrophy was discussed at the weekly clinicopathological conference at the Massachusetts General Hospital.[14] He was a young man of twenty-four who had had muscular dystrophy since the age of eight. He died with cardiac hypertrophy and dilatation, mural thrombi of the left ventricle and renal and splenic infarcts. The myocardium showed the same changes found in the dystrophic skeletal muscles, that is, fibrosis and infiltration of fat between the muscle fibers.

Tyler and Wintrobe[15] believe that the fact that creatinine is absent and creatine increased in muscular dystrophy is an argument for a specific biochemical lesion in the metabolism of muscle. They pointed out that the peculiar pattern of dystrophic muscles is related to the age at which the anlage of a particular muscle appears in the embryo. Ulick and Milhorat[16] discussed the chemical nature of a factor in hog-stomach extracts that reduces the creatinuria of muscular dystrophy. The tocopherols had no effect in man, although they do abolish the creatinuria of the muscular dystrophy of experimental vitamin E deficiency. Synthetic alpha-tocopheryl-p-hydroquinone duplicated the activity of a treated fraction of gastric mucin.

A practical suggestion for treatment of muscular dystrophy was offered by Young.[17] He devised a self-raising chair equipped with two strong springs on the under side of the seat and a cane with a 3½-inch block of wood or a hollow metal square attached to the end. The patient steps on the block with one foot and raises himself on the other leg. The block can also be used as the handle of the cane. Mayerhofer[18] treated children of school age with 2 or 3 daily intramuscular injections of 4 to 7 units of insulin, believing that dystrophy has a diabetic component. Excellent results were obtained, particularly in early cases in which hypertrophy of muscles had not yet appeared. Actual cure of the disease by means of insulin was not established.

In 1950 two foundations for the study of muscular dystrophy were chartered in the United States of America — one in New York and one in Texas.

Myasthenia Gravis

In Children

Fulminating type. The disease may have a fulminating course, as noted by Bastedo[19] in the case of a ten-year-old child. In less than a day the child developed dysphagia, dyspnea, cyanosis and collapse, similar to the symptoms of acute bulbar poliomyelitis. The response to neostigmine methylsulfate (0.5 mg. given subcutaneously) was immediate and complete. Subsequent treatment with neostigmine bromide, by mouth, was satisfactory, and the patient became symptom free, on 3 15-mg. tablets a day, in six weeks. Bastedo found examples of 44 cases of myasthenia gravis in children in the literature; 3 had an acute onset. The author thinks that a neostigmine test is indicated in all acute respiratory disturbances in which the nature of the causative factor is not fully established.

Treatment. Ritter and Epstein[20] treated a nine-year-old child with neostigmine, thymectomy, adrenocorticotrophic hormone and cortisone. The patient showed a steady downward clinical course, unaffected by treatment, and died in eight months. The authors believe that the prognosis in children is poor, in contrast to the opinion of most other investigators. The progressive, unremitting type of myasthenia gravis is not unknown, but it is rarely encountered, particularly in children. A more typical response after thymectomy was obtained by Tunestam[21] in a nine-year-old child. Recovery was prompt. Bowman[22] reported on 3 patients, seen in 1947, aged three, four and eight years respectively. One had symptoms at birth; now seven years of age, the patient is nearly symptom free. No evidence of myasthenia gravis was found in the parents or family. The second and third patients were cousins; they, too, were in good health in 1951. Bowman believes that all infants and children with ptosis should have a neostigmine test.

Congenital myasthenia. In addition to the case reported by Bowman,[22] Levin[23] noted two more cases. He thought, moreover, that the disease process became clinically evident before birth. The prenatal manifestations were a delay of quickening and a reduction in the amount of fetal activity. One patient died at ten years of age, of pneumonia; neostigmine had been withheld during the acute illness. The other patient made a full recovery. In neither case was the disease intermittent or characterized by relapses. The children were brother and sister.

Neonatal or transitory myasthenia. Geddes and Kidd[24] observed severe myasthenic symptoms in a newborn child of a myasthenic mother. Under treatment with neostigmine for slightly over five weeks recovery was complete. The mother, who had had a thymectomy, did poorly during pregnancy and died in a respiratory crisis about three weeks after delivery. The authors found 6 other cases in the literature; all these children were born to myasthenic mothers. All the infants showed signs at birth or within three days. Four of the 6 survived. One of us (H.R.V.) has observed three similar cases, all with excellent recovery. The condition is not uncommon; in our series it occurred in 3 out of 36

cases. The transitory myasthenia of the newborn should be clearly differentiated from the congenital type. Holt and Hansen[25] added an excellent account of another example of neonatal myasthenia in a Negro child. The patient, known to have myasthenia, was reported by Stone and Rider.[26]

Diagnosis

Muscle relaxants. In spite of its potential danger in myasthenia gravis, curare may be of occasional value in making the diagnosis, as shown by the case reported by Beamish and McFarlane.[27] A Chinese man of fifty-seven nearly died when curare was given as an anesthetic during a laparotomy. Artificial respiration was needed before recovery took place. The myasthenic aspect of his illness was not recognized at the time. Eight months later, orally administered neostigmine was found to aid respiration during an attack of pneumonia. The curare test was then made, followed by a neostigmine test, with a favorable response. The authors report by letter that the patient was in complete remission eight months later. Dundee[28] has suggested the use of an even more dangerous drug — gallamine, or flaxedil. Used as a muscle relaxant in anesthesia, it may cause prolonged intercostal paralysis. Its use cannot be recommended. Quinidine and quinine are also hazardous and should be avoided in both diagnosis and treatment.[29]

Dysphagia. Viets[30] noted the response to neostigmine as observed under the fluoroscope when the act of swallowing was visualized. The response occurred in fifteen to thirty minutes, with emptying of the pyriform sinuses and the valleculae, normal constriction of the pharyngeal muscles and removal of most of the medium-thin barium paste from the walls of the pharynx. The test is positive only in myasthenia gravis.

Intravenously administered neostigmine. Tether,[31] administering 0.5 mg. of neostigmine methylsulfate intravenously, developed a rapid test for myasthenia gravis. The principle is the same as the diagnostic test first used by Viets and Schwab in 1935, except that the drug is given intravenously without atropine. The response is rapid, occurring within a minute or two. No serious reactions were observed by Tether.

Toxicity

After diagnostic test. Merrill[32] reported on the death of a thirty-nine-year-old man after the intramuscular injection of 1.0 mg. of neostigmine methylsulfate. A generalized convulsion occurred five minutes after the administration. In ten minutes respiratory difficulty was noted; in fifteen, shock; in fifty minutes, death. The patient had responded slightly to 0.4 mg. of atropine sulfate. No cause of death, other than shock, was disclosed at autopsy. In the initial injection atropine was not used, but this does not explain the death, as Tether[33] has used neostigmine intravenously, without atropine, since 1942. The death in Merrill's case, the only one recorded in the literature, is unexplained.

THE THYMUS GLAND AND THYMECTOMY

Histopathology

Bratton[34] examined the thymus after its surgical removal in 70 cases. He found, by comparison with normal glands, that there was no evidence of "persistence" in myasthenia gravis. Germinal centers of lymphocytes in the cortical nodules were found in 66 out of 70 cases — but in only 3 of the nonmyasthenic controls. Thymomas were present in 13 out of 70 (18.8 per cent). Occasionally they metastasized locally. Similar findings were reported by Castleman and Norris,[35] studying the Viets series in addition to post-mortem and biopsy material and 295 cases from the literature. Included were 112 thymectomies reported by Keynes. Thymoma was found in nearly 30 per cent of the entire group. In most recent series (operative) the percentage has been about 15. Ten per cent of the thymomas show local implants, but no true metastases were found. "Germinal centers" were observed in 75 per cent; they were not demonstrated in the normal thymus. Reid[36] found changes of the same type in his short series. Seybold,[37] using Mayo Clinic statistics, found thymomas in 15 per cent, but 25 per cent of the tumors examined had occurred in patients without evidence of myasthenia gravis. Most tumors had a distinct fibrous capsule; none metastasized beyond the local structures. No tumors recurred.

Thymectomy

Removal of the thymus gland in myasthenia gravis was carried out in many surgical clinics. Keynes[38] operated on 155 myasthenic patients, with 65 per cent complete or nearly complete remissions. The operative mortality in his series was less than 5 per cent. Thymomas occurred in 11.6 per cent of the 155 patients. Viets[39] reported on 36 thymectomies. Seven patients had thymoma; 3 were living, one having survived six years. Of the non-neoplastic series, 45 per cent were in full or good remission. Eaton,[40] with 46 thymectomies, found a 60 per cent remission rate. About 15 per cent of the whole group had thymomas. Whiteside and Weder[41] had two excellent results; Gatenby,[42] one; and Kooreman,[43] two. Nursing care was emphasized by Keynes.[44]

Thymectomy for Thymoma

Relatively few patients with thymomas have responded rapidly after removal. An exception was reported by Peyser,[45] whose patient needed no neostigmine after twenty-four hours and was well in ten days. No relapse had occurred in ten months. Reid and Marcus[46] reviewed all the thymoma cases up to 1947, beginning with Weigert's autopsy find-

ing in 1901. Twenty-nine patients had been operated on in cases of myasthenia gravis; 18 were available for study. Of these, 9 were benefited; 5 died after operation.

Roentgen Therapy

Halberstaedter and Hochman[47] treated a patient with deep roentgen rays, the tumor having been disclosed by roentgen examination. The tumor disappeared; the patient was free from symptoms. Welte[48] treated 3 cases successfully. Most other investigators reported unsatisfactory results, and in many clinics x-ray treatment was abandoned.

ACTH and Cortisone

Millikan and Eaton[49] treated 5 cases at the Mayo Clinic. Two showed no improvement; 1 was slightly better; 1 was moderately improved; and the fifth was considerably improved. The authors concluded that the hormones were of limited value in treatment of the disease.

Myasthenia Gravis and Hyperthyroidism

Taylor and Large[50] treated a patient who had both conditions. The hyperthyroidism was first completely controlled by propylthiouracil and did not recur. The myasthenia was poorly controlled by orally and intramuscularly administered neostigmine. Thymectomy was followed by an excellent remission, and the patient was fully rehabilitated for a two-year period.

Cholinesterase Inhibitors

DFP and Cholinesterase

Wilson, Maw and Geoghegan,[51] using di-isopropylfluorophosphonate (DFP), found that the effect was localized when a single dose was injected into the brachial artery. Under prolonged administration additional muscle groups were affected, but the addition of neostigmine caused a marked increase in the intensity and extent of clinical improvement. They believed that DFP was not a suitable or reliable drug for the routine treatment of myasthenia gravis. The clinical improvement noted after treatment with DFP could not be directly correlated with the degree of inhibition of either red-cell or plasma-cholinesterase activity. This was also so with neostigmine. Neither test could be used as a reliable index of the inhibition of cholinesterase at the neuromuscular junction. In a second paper, Wilson, Maw and Geoghegan[52] pointed out that the activity of pseudocholinesterase in plasma and that of true cholinesterase in red cells did not differ significantly in range or in mean value in myasthenia gravis from that observed in 100 normal subjects. These results strengthen the conclusion that the metabolic defect in myasthenia gravis does not lie in an abnormally rapid destruction of acetylcholine. Goldstein and his associates[53] also found that the inhibition of the plasma enzyme after administration of neostigmine bore no causal relation to the pharmacologic action of the drug. It was also pointed out that neostigmine was only partially absorbed when administered orally. The oral dose had only one thirtieth the effect of its parenteral administration. Recovery from the stool was negligible. It appears that the drug is largely inactivated in or by the gastrointestinal tract.

TEPP

Grob and Harvey[54] thoroughly investigated tetraethyl pyrophosphate. Of twelve patients studied, 9 were able to be maintained for periods of one to eight months. All had better strength and endurance than during the administration of neostigmine. Three of the 9 had moderately severe nausea, not entirely relieved by atropine. After a few months of TEPP they returned to neostigmine. Six patients remained on TEPP. There were many difficulties in adjustment. The dangers of overdosage and the minimal effects of underdosage made it impossible to use the drug in half the cases treated. These clinical results were confirmed by Koelzer and Giesen[55] and Atkinson.[56]

OMPA

Octamethyl pyrophosphoramide was used by Rider and his associates.[57] They found the drug stable and relatively nontoxic. It could replace neostigmine in some cases. Only two oral doses were required per day. Of six clinical trials, four were successful. Action was smooth and sustained. Toxic side-effects were frequent but mostly occurred during the period of transition from neostigmine to OMPA. When maintenance on OMPA alone was established, side-effects were negligible and were readily controlled by atropine. Patients with severe myasthenia who were not improving on neostigmine showed no improvement on OMPA. One of the 6 patients died of respiratory failure. Serum and red-cell cholinesterase tests were useful in controlling dosage.

Pregnancy

Variations in response to pregnancy continued to be reported in the literature. Some patients have become worse during pregnancy, even relapsing to a point where cesarean section was indicated two weeks prior to term, as reported by Harris and Schneider.[58] Gunn and Sanderson[59] had similar experiences with two patients. On the other hand, Olson[60] had a patient with complete remission from the fourth month to term, and Amelung and Lorenz[61] noted a striking regression of symptoms in their patient during the last half of pregnancy.

Miscellaneous Topics

Carotid-Sinus Removal

Reports from France, the Continent and South America continue to appear. Procaine block has

sometimes given temporary improvement. Bilateral operation was helpful in two cases reported by Strnad.[62] Immediate response was recorded by Pintus and his associates.[63] The child with fulminating myasthenia operated on by Chigot (reported by Weill[64]) died in twenty-four hours. At autopsy the thymus was hyperplastic. The operation is still experimental and of doubtful value.

Dental

Keeling[65] discusses the history of 4 patients with weakness of the jaw; one had a thymoma by x-ray examination. Three responded rapidly to the neostigmine test of Viets and Schwab.

Myasthenic Crisis

Korey and Randt[66] treated 3 patients in respiratory distress, with one death. They thought that patients with marked weakness of vital muscle groups, unimproved by 1 to 2 mg. of neostigmine by injection every hour for three to five doses, should not receive further continuous treatment. The minimal response may cause out-of-phase breathing in the respirator, and neostigmine enhances bronchial secretions. Treatment should be supportive, — by respirator or tracheotomy or both, — until spontaneous remission occurs. The two patients who recovered were drug-free for three and eleven days. The patient who died had a thymoma, as revealed at autopsy.

Early Symptoms

Weisman[67] had a patient whose chief symptom for years was palpitation. When she became worse on quinidine and dysphagia developed, the diagnosis was made. Palpitation disappeared under treatment with neostigmine.

Trial Drugs

Simon[68] used Pitocin (containing the oxytocic principle of the posterior lobe of the pituitary gland) in one case, with recovery. Maou had similar results. (Both patients might easily have had a spontaneous remission.) Rudd and Cullinan[70] used effectively a tetanizing current to treat the fatigued masseter muscles; Stern[71] used anaphylactic shock, with horse serum given intravenously.

Associated Diseases

Perry[72] found a patient with diabetes mellitus; Trelles, Barrère and Roedenbeck[73] observed a high familial incidence of mental disease, epilepsy and alcoholism in the ophthalmoplegic form of myasthenia; Barbey[74] noted myasthenia following diphtheria; and Störtebecker[75] found infection, as indicated by lymphocytosis, in two thirds of his cases. Thévenard[76] observed myasthenia after injection of antitetanic serum. Guinet, Girard and Bonnet,[77] in an excellent review, reported that myasthenia gravis and hyperthyroidism are rarely associated and that when both conditions coexist in the same patient the prognosis is grave. This is not always the case, as noted by Taylor and Large.[50] Myasthenic symptoms are common in hyperthyroidism. They disappear under appropriate treatment for Basedow's disease.

Insurance

Weisman[78] found myasthenia similar to diabetes, as far as insurance is concerned. Both respond to proper maintenance therapy.

Experimental

Constant, Porter, Andronis and Rider[79] studied the effect of thymic extract on neuromuscular response. Extract from glands of two patients with myasthenia and nonmyasthenic extract from one patient were used. When injected into the general circulation of a cat, diminished muscular contractions, as compared with the normal, were obtained. Splenic extract augmented the contractions. Lesny[80] noted fatigue in guinea pigs after injections of blood from myasthenic patients.

Distribution

Refsum[81] found that 58 cases had been recorded at the Oslo Clinic since 1912.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 37431

PRESENTATION OF CASE

A fifteen-month-old girl was admitted to the hospital because of jaundice.

One month prior to admission while cutting the bicuspids the child developed bilateral swelling under the chin, low-grade fever and some reddening of the right eardrum. She was treated with ear drops and a sulfonamide compound for three days, with subsidence of the symptoms. At about this time she was observed to be scratching her skin a great deal but otherwise appeared well. No jaundice was noted. Six days prior to admission a red blotchy rash developed over the neck and face. She was afebrile. At this time the mother noticed that the scleras had a yellowish tint and that the abdomen was becoming larger. In the following two days there was a rapid increase in jaundice. The patient's appetite during this period seemed to improve, and she was quite active. Two days prior to admission she was seen by a physician and placed on skimmed milk. Thereafter the stools, which previously had been somewhat loose but of normal color, became hard, pale and infrequent. No stools were noted on the day before admission.

The child had had a normal birth and neonatal period, with a birth weight of 6 pounds and 3½ ounces. The pregnancy had been uncomplicated. She had been breast fed for two weeks and then was switched to a whole-milk and Karo Syrup formula and at about one year chopped foods were added to the diet. She received oleum percomorphum, 10 drops, until the age of thirteen months. She was immunized against diphtheria, pertussis and typhoid between her sixth and eighth months but was not vaccinated. For one month following the loss of the cord stump there was recurrent change at the umbilical site, which healed after treatment by repeated cauterizations.

Physical examination revealed a 29-inch, 23-lb., well developed, jaundiced child who was listless and irritable. The scleras were yellow tinged. The skin was distinctly yellow with a few faint red macules at the upper chest. The pharynx was negative. The lungs were clear. The heart was of normal size with a Grade II apical systolic blowing murmur that was not transmitted. The abdomen was protuberant and a firm, smooth, nontender, 14-by-19-cm. mass was felt in the right upper quadrant that extended into the left upper quadrant just to the left of the midline. The mass extended into the right flank posteriorly and apparently occupied almost the entire right side of the abdomen. It was thought to be separate from the liver, which could be felt 2 fingerbreadths below the costal margin and had a sharp nontender edge. The spleen was not felt. No fluid was noted.

The temperature was 98.4°F., the pulse 116 and the respirations 48.

The urine gave a ++ test for albumin and a + test for bile; the sediment contained an occasional red cell and hyaline cast and 50 white cells per high-power field. Examination of the blood revealed a hemoglobin of 10.9 gm. and a white-cell count of 18,700, with 56 per cent neutrophils, 39 per cent lymphocytes and 5 per cent monocytes. On smear the red cells varied in size and there were many target cells and a rare stippled cell. The prothrombin time was 16 seconds (normal, 19.5 seconds).

X-ray films of the chest revealed clear lung fields with diaphragms elevated by a large intra-abdominal mass. Abdominal films showed a large soft-tissue mass present in the right side of the abdomen that had displaced the stomach and small and large intestine to the left. The mass was smoothly rounded and could not be separated from the liver shadow but could be separated from the kidneys, which appeared of normal size. Intravenous pyelogram showed the dye to be well concentrated, outlining nondilated urinary passages on both sides (Fig. 1). There was a suggestion of a small amount of fluid in the peritoneal cavity.

The patient passed several clay-colored stools while in the hospital. Her condition remained unchanged. She refused almost all food other than milk. On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. CLAUDE E. WELCH*: When I received this protocol several days ago I gave it to my twelve-year-old son to read over. I wondered if he could help me with the diagnosis inasmuch as he gets all his medical information from the *Reader's Digest.* I asked, "What do you think it to be?" He said, "It is a cyst." I said, "What is in the right upper quadrant?" He replied, "The bile ducts." With that as a preliminary diagnosis I shall consider the

*Associate visiting physician, Massachusetts General Hospital.

possibility of a congenital cyst of the bile ducts, which is one of the commonest causes of these particular symptoms.

The history was not very characteristic or informative until just before the patient came into the hospital. The jaundice of six days' duration obviously had come on rather rapidly because nothing had been noted previously except a slight amount of scratching, which suggested a low-grade jaundice. Although the presence of a previous acute infection and the sulfonamides are of interest, I do not think they are important to our discussion. Then the abdominal mass began to become apparent and

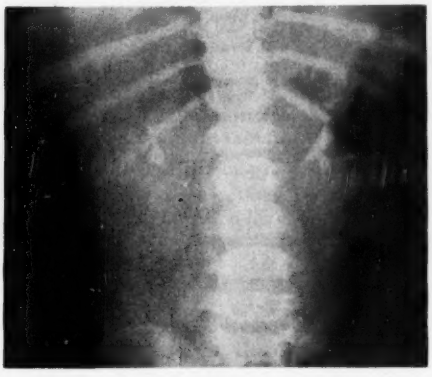

FIGURE 1.

there were clay-colored stools. The examination in the hospital gave objective evidence of jaundice and began to localize the disease. There was nothing remarkable in the past history. There was no suggestion of a chronic wasting disease. The child was well and her weight was approximately normal. She entered the hospital with a firm smooth nontender mass in the right upper quadrant that extended across to the left side. The description of this mass is extremely important. I do not think I can expand on it as it obviously was described very carefully. There was no fever. The blood count was not too remarkable for a child of this age — that is, it certainly was not diagnostic. Except for the bile in the urine there was little evidence other than that the child was sick.

DR. BENJAMIN CASTLEMAN: Here is a drawing of the mass made by the resident.

DR. WELCH: In this drawing a large mass is shown extending down below the umbilicus, halfway over to the left hypochondrium and halfway down to the inguinal ligament and apparently lying all anteriorly rather than posteriorly.

Being faced then with an abdominal mass in a child a little over a year old, I have three major possibilities to consider. One is the presence of some malignant tumor of which an embryoma of the kidney is the most common. There are other malignant tumors that I shall also have to consider. The second and third most common diagnoses are congenital cyst of the biliary tree and duplications of the intestinal tract — in this area particularly of the duodenum. With these three possibilities in mind, let us see the x-ray films.

DR. JAMES J. MCCORT: The palpable soft-tissue mass is seen filling almost the entire right abdomen and displacing the intestines, to the left and downward. It is smooth in outline, lying somewhat anteriorly as described in the physical examination, and shows no calcification. Also it seems to be separate from the liver edge laterally, but anteriorly I cannot separate it from the shadow of the liver. A film of the abdomen was obtained in the lateral decubitus position to see if the mass would fall away from the edge of the liver and if there was any layering of fat within it. Neither of these was found.

On intravenous pyelogram the kidneys are normal in size, position and shape; they excreted the dye promptly and there was no obstruction to either urinary passage. The mass is entirely separate from the urinary tract (Fig. 1).

DR. WELCH: There was no drink of barium I presume?

DR. MCCORT: No.

DR. WELCH: The x-ray findings are very helpful, particularly from the point of view of excluding a tumor of the renal tract. Let me consider first the possibility of some malignant tumor. Admittedly the differential diagnosis of a malignant tumor of children of this age is particularly difficult. If the patient had entered the hospital with the well marked cachexia that one might expect with a tumor of this huge size, then the diagnosis would be clear; but she was quite well developed and nourished, so I have no evidence from that point of view that she had a malignant tumor. Of malignant tumors that she may have had, a Wilms tumor is eliminated by the normal intravenous pyelogram. As I mentioned before, that is the commonest large malignant tumor in children. Years ago we had in this hospital a child of this age with a huge fibrosarcoma of the left lobe of the liver. As we know, other very bizarre tumors may appear in children of this age and may grow very rapidly. It is conceivable that this could have represented such a tumor, which was pressing up on the bile duct to produce the jaundice. This mass by x-ray examination seemed to be independent from the lobe of the liver and therefore a tumor originating in the liver can be ruled out. Another possibility that I ought to consider is a tumor aris-

ing from the sympathetic ganglia, such as a ganglioneuroma arising from the region of the right adrenal gland. Again there was no evidence in favor of that because there was no displacement of the kidney. I am not very well pleased with the diagnosis of malignant tumor.

I think it is more likely that I am dealing with a congenital abnormality. The most common congenital abnormalities that I have to consider are the congenital cysts of the bile duct and duplications of the duodenum. There is some evidence in favor of the cyst of the bile duct on several bases; one is the frequency of the two diseases. When Dr. Gross[1] collected his first series of duplications of the duodenum, for example, he was able to find only one of those cases in the Children's Hospital records and was able to collect some 50 cases of congenital cysts of the bile ducts. Over ensuing years, congenital cysts of the bile duct are becoming considerably more common than duplication of the duodenum. The duodenum is one of the rarer parts of the intestinal tract to be duplicated. It is quite clear that any duplication would have had to be of the duodenum to explain the jaundice; that is the one tumor other than the cyst of the biliary tree that can produce jaundice.

Then I have some evidence from the symptomatology of the patient. When duplications of the duodenum occur (and cysts of the head of the pancreas and paraduodenal cysts all should be put in the same group), the patients usually have symptoms of duodenal obstruction. Jaundice is uncommon with the duplications. On the other hand, patients with cysts of the bile ducts have a triad of symptoms that consists of abdominal pain, jaundice and a mass. The pain was not well marked in this particular child, but it would be rather hard to elicit anyway. She was becoming irritable; that possibly represented a mild degree of pain. She certainly had a mass and she certainly had jaundice. Consequently from the point of view of symptomatology this diagnosis would fit perfectly well.

I suppose she did have a cyst of the common duct; that of course could be manifested at her age. If these patients have a complete atresia of the bile ducts, the diagnosis is often made in the first two or three days of life. Dr. Nathan Talbot tells me this diagnosis is not always easy, since several days may elapse before jaundice is definite. If there is a simple cyst the diagnosis may be made at any time — even in adult life. It is of interest that one of the early patients on whom the diagnosis was made about twenty-five years ago is now in the hospital again. She has had repeated operations on the cyst of the common duct and now has a carcinoma of the head of the pancreas, perhaps indicating that there is more wrong congenitally than is suspected. Embryonic rests may be present as well as the cysts.

It is of interest to speculate on what influence the infection may have had on the onset of the symptoms. Many of these patients at operation or at autopsy are found to have patent ampullas of Vater. The infection may have been just enough to produce an obstruction at that site. Some of these patients have a condition that is probably analogous to an achalasia of the esophagus or colon in that everything appears to be perfectly normal except for the absence of nerve cells. At any rate, the etiology is far from clear. The treatment is more standardized. I believe that when the surgeon explored this girl he found a cyst of the bile duct that he anastomosed in some fashion to the intestinal tract.

Clinical Diagnosis

?Enterogenous cyst (duplication of duodenum).

Dr. Welch's Diagnosis

Congenital cyst of common bile duct.

Anatomical Diagnoses

Congenital dilatation of common bile duct (choledochal cyst).

Obstructive cirrhosis of the liver.

Pathological Discussion

Dr. Castleman: I am sorry that Dr. Robert R. Linton, who operated on this child, cannot be here. His preoperative diagnosis was a duplication of the duodenum. At operation, he found a cyst of the common duct, as Dr. Welch predicted (Fig. 2). This anomaly probably should not be called a choledochal cyst because it is really a part of the wall of the common bile duct that has become markedly distended apparently due to some congenital weakness in the wall. Gross and Ladd[2] prefer to call it congenital dilatation of the common bile duct. The dilatation of the common duct contained over a liter of bile, which was removed through a window

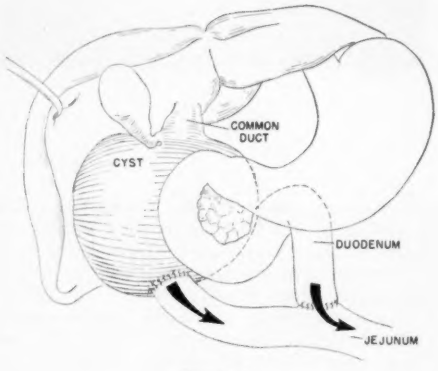

Figure 2.

in the wall; bile was seen coming down from the liver through a very small lumen. The bile was drained through a T-tube and an anastomosis made with the jejunum. The liver at the time of operation was grossly cirrhotic and a biopsy showed moderate bile stasis and definite obstructive cirrhosis — fibrosis and bile-duct proliferation. The amount of bile-duct proliferation was much more than one would expect with the short period of jaundice that she apparently had.

The follow-up on this patient is interesting. She continued to be jaundiced for about two weeks; the jaundice then gradually decreased until about three and a half weeks after operation, when the stools became tan and the jaundice disappeared. She was sent home with the T-tube still in place, to be left there for about six weeks for adequate decompression. I understand from a surgical point of view that in these cases no attempt should be made to remove the cyst.

DR. WELCH: They are impossible to remove and the patients have usually done very well following anastomosis.

DR. KRANES: Where does the obstruction arise in these cases? In the site of entrance into the duodenum?

DR. CASTLEMAN: Usually it is in the lower end just proximal to the ampulla; the weight of the dilated and full sac produces a kink in the common bile duct.

ADDENDUM

DR. ROBERT R. LINTON: I wish to compliment Dr. Welch on making the correct diagnosis. From the surgical point of view, the chief point of interest is the type of anastomosis that was utilized. In most cases in the literature a direct choledochoduodenostomy has been performed, whereas in this patient a choledochojejunostomy using the Roux-Y approach was performed. In the former ascending biliary infection is frequently a serious complication. It was hoped with the type of anastomosis used in this case that it might be possible to prevent it. The drainage tube is still in place and it is our plan to have the patient return in a month for a cholangiogram. Whether further surgery will be performed or not will depend a great deal on the findings at that time.

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CASE 37432

PRESENTATION OF CASE

A forty-year-old male wool worker was admitted to the hospital because of fever of eight weeks' duration.

The patient was well until about eight weeks prior to admission, when he began to perspire more than usual and noticed fatigue and lassitude. He was found by his physician to have a fever. Eighteen days before entry he was admitted to another hospital, where he continued to run a spiking temperature with double rises daily, in spite of courses of treatment with penicillin, aureomycin, Chloromycetin and streptomycin. After some days of penicillin therapy, he developed a diffuse erythematous eruption over the trunk, arms and thighs, which disappeared when penicillin was discontinued and reappeared when penicillin was resumed two days prior to admission. At this time the spleen became palpable and the liver was felt 2 fingerbreadths below the costal margin. After a rectal examination he noted a small amount of blood on the toilet tissue, but there was no other rectal bleeding and no tarry stools or hematemesis. Laboratory studies on admission to the other hospital showed a hemoglobin of 76 per cent and a white-cell count of 3450 per cu. mm. The hemoglobin had dropped to 50 per cent the day before admission here and the white-cell count varied between 3250 and 6000. Three differential counts were normal, but the red cells were "microcytic to normocytic" and "hypochromic to normochromic." Blood cultures, agglutination tests for typhoid, paratyphoid and brucellosis, Weil–Felix test with Proteus OX-19 and OX-2 complement-fixation tests for murine typhus, Rocky Mountain spotted fever and Q fever were all negative.

The patient had lived in New England all his life. He stated that he had had frequent drenching night sweats for twenty years. Twenty years before admission he had a radical mastoidectomy for a chronic draining ear, followed by lateral sinus thrombosis, bilateral septic pulmonary infarcts and bilateral empyema, the latter requiring bilateral surgical drainage. On two other occasions, six and a half and two years prior to entry, he had high fever, again requiring drainage of the empyema cavities. One brother had tuberculosis eight years before the patient's admission but was not in contact with the patient.

Physical examination showed a well developed but emaciated man who appeared acutely ill. The skin was hot, moist and pale, with a widespread erythematous, morbilliform, macular rash over the trunk, arms and thighs and an enanthem on the roof of the mouth. A few of the areas over the back were hemorrhagic. There were faint scleral icterus, a right-mastoidectomy scar and a large perforation of the right eardrum. Several small soft, freely movable, nontender cervical, axillary, inguinal and femoral lymph nodes were felt bilaterally. Both lung bases were slightly dull, with diminution of breath sounds, especially in the region of the surgical scars, and a few crackling rales, more noticeable on the right. Frequent cardiac premature

beats were heard. The abdomen was distended and tympanitic. The liver could be felt 2 to 5 fingerbreadths below the right costal margin; it was smooth, firm and nontender, with its upper border at the sixth intercostal space. The spleen was palpable 2 fingerbreadths below the left costal margin and was also firm, smooth and nontender. One observer noted on rectal examination, on straining, a fairly soft, vertically placed mass above the prostate. Both knee jerks were absent.

A urinalysis showed a specific gravity of 1.026, a ++ test for albumin, an orange sugar test (specimen was obtained during an intravenous infusion of glucose) and a + test for bile; the sediment contained rare red cells, rare white cells and rare hyaline and granular casts. Examination of the blood revealed that the hemoglobin was 10.3 gm. and 9.4 gm. and the red-cell count 2,760,000, with 8 per cent reticulocytes. There was considerable achromia of the red cells, occasional polychromatic red cells, occasional stippled cells and considerable variation in shape and size of the red cells, most of them appearing larger than normal. The white-cell count was 2900, with 88 per cent neutrophils, 6 per cent lymphocytes, 2 per cent monocytes, 1 per cent eosinophils, 1 per cent late myelocytes and 2 per cent young neutrophils. The hematologist did not confirm the presence of immature cells. The platelet count was 150,000 per cu. mm. Aspiration bone marrow from a spinous process was intensely hyperplastic, with a myeloid–erythroid ratio of 0.6:1 and with an increased number of megakaryocytes without platelet formation. Reticulum cells were markedly increased. An erythrocyte-fragility test showed no hemolysis in 0.5 per cent sodium chloride. The blood sugar was 108 mg., the albumin 2.85 gm., the globulin 1.62 gm., the bilirubin 3.9 and 5.4 units direct and 5.6 and 7.5 units total and the nonprotein nitrogen 21 mg. per 100 cc.; the sodium was 124.8 and 118 milliequiv., the chloride 98 milliequiv. and the potassium 4.4 milliequiv. per liter. The cephalin flocculation was + in 48 hours and the prothrombin time 78 per cent of normal. A Coombs test, Widal test and blood Hinton test were negative and a blood culture showed no growth. A stool urobilinogen was normal and a urine urobilinogen was 24.5 Ehrlich units. Two stool guaiac tests were negative.

X-ray films of the chest with fluoroscopy showed that both leaves of the diaphragm were elevated laterally and partially fixed to the chest wall by old adhesions. There was some pleural thickening in the lower chest, particularly along the right lateral chest wall. Diaphragmatic excursions were normal. Old operative defects were noted in the right ninth and left eighth and ninth ribs. There was some soft-tissue calcification laterally, opposite the left seventh rib. The lung fields were clear and cardiovascular shadows were normal. A film of the abdomen showed no enlargement of the liver or spleen. The upper right psoas shadow was not identified.

Two days after admission the skin eruption was improved. Icterus was more apparent. On the sixth hospital day a white-cell count was 1000, with 76 per cent neutrophils, 16 per cent lymphocytes and 8 per cent monocytes. On the seventh day an alkaline phosphatase was 12.5 units per 100 cc. The next day the serum sodium was 129.1 milliequiv. and the chloride 101 milliequiv. per liter. On this day, the patient was started on ACTH (adrenocorticotrophic hormone), 25 mg. intravenously daily for four days, then 50 mg. daily for two days. He was then started on cortisone, 110 mg. orally every eight hours, without significant improvement.

On the tenth hospital day the patient passed several clots of blood in a stool. He continued to run a constantly elevated temperature, varying from 99°F. to 104.5°F. with no consistent daily pattern.

The white-cell count continued around 1000 to 1500 per cu. mm. and the hemoglobin dropped progressively to a low of 5.3 gm.

On the fifteenth hospital day an operation was performed.

Differential Diagnosis

Dr. Daniel S. Ellis*: I should like to know whether the liver could be felt 2 or 5 fingerbreadths below the costal margin or whether it is true that it varied.

Dr. F. Dennette Adams: The variation was between expiration and inspiration. May I make another comment that might help, Dr. Ellis? The statement that the hemoglobin dropped to 50 per cent the day before admission is misleading. The drop was gradual — not sudden.

Dr. Ellis: If measurements of the liver are accurately made and the upper border is recorded as

*Assistant physician, Massachusetts General Hospital.

being at such and such a level and the lower border so many centimeters below the costal margin in the midclavicular line, so many centimeters below the xiphoid and so many centimeters to the left of the midsternal line at inspiration then there is no question about the size, but most physicians are in too much of a hurry to make such measurements. In this particular case the upper border of the liver was at the sixth rib and was actually felt 5 fingerbreadths below the costal margin. I believe this liver was enlarged in spite of the x-ray findings. I think the size of the liver reported by the radiologists frequently is not accurate; usually they do better in estimating the size of the spleen. If I felt the liver to be large and could flip its edge I would depend on that more than on what Dr. McCort thought about it from viewing the x-ray films alone; there is no argument, both methods of measurement are inaccurate.

Dr. Adams: Several observers believed that both the liver and spleen could be easily felt.

Dr. Ellis: That brings up the question whether or not a palpable liver and spleen mean a large liver and spleen. Again the two do not always go hand in hand. The fact that the right psoas shadow was not identified may or may not be important.

I have tried to visualize what a vertically placed mass above the prostate may have been, but such a description "leaves me cold."

Dr. Adams: May I also add that you can disregard that questionable mass in the rectum. It was never confirmed.

Dr. Ellis: It seems to me there is enough evidence that the skin eruption that was associated with the administration of penicillin, which disappeared when penicillin was stopped and then recurred when the penicillin was reinstituted, was a penicillin rash and I shall not pay any more attention to it.

The first time I read this case, I wanted to go back to Maine, where I had been on vacation. I had no idea what this patient had and I might add, having read it several times since, that I doubt if anybody knew what he had at the time he was operated on. Furthermore, I am in a quandary as to what operation was done on this patient with a hemoglobin of 5.3 gm. The hemoglobin apparently had been falling steadily and in the few days before operation the fall had been accelerated by what was apparently a brisk enough bleeding by rectum to give him blood clots. There was no mention made of this patient's bowel habits. I wonder whether he had diarrhea or whether he had any abdominal pain. If he was bleeding by rectum, — passing clots of blood, — I would think he warranted a sigmoidoscopy. Perhaps the operation was a sigmoidoscopy with biopsy, perhaps it was a biopsy of the lymph node or perhaps it was a liver biopsy. Maybe more was known than I have been told and the operation was a laparotomy to find out the cause of the bleeding. I do not believe anyone would be willing to operate on a patient with a hemoglobin of 5.3 gm. without giving him transfusions. I would not have been willing to do a liver biopsy on a patient with a hemoglobin at that level under usual circumstances. Therefore, that leaves a biopsy of the rectal lesion or a lymph node, which might have been done with safety.

Dr. Benjamin Castleman: An aspiration liver biopsy was the operation.

Dr. Adams: He had several transfusions beforehand.

Dr. Ellis: I am left with the problem of explaining a fever of long duration, progressive anemia, hepatomegaly, splenomegaly and leukopenia. The history of sepsis in the past and of recurring sepsis up until two years before the present episode makes me want very strongly to believe that he again had an active pyogenic infection somewhere that was causing the fever. The persistent leukopenia is against that, to my mind. I find it hard to believe that a patient would have pyogenic infection, localized abscess, osteomyelitis or pylephlebitis of the liver and still consistently run a white-cell count of 1000 unless he had some old change affecting the bone marrow. If he had enough response to infection to produce fever, which he had, I should think with a normal bone marrow he ought to have enough resistance to raise the white count.

Dr. Jacobson tells me that the increased reticulum-cell count in the bone marrow is nonspecific. It might mean leukemia or something else in the bone marrow. The rest of the bone-marrow report to me is consistent with an attempt to replace blood that had been chronically lost. I see nothing in it to indicate that there had been actual replacement of marrow by neoplasm unless the increased reticulum-cell count was a response to neoplasm. If Dr. Jacobson has any help for me I should like it.

Dr. Bernard Jacobson: These findings are nonspecific phenomena and are consistent with chronic

infections such as tuberculosis and also are common in various forms of lymphoma.

DR. ELLIS: I shall rule out chronic sepsis on the basis of persistent leukopenia and no evidence of localizing signs.

The patient had jaundice, splenomegaly and hepatomegaly. I wonder whether he may have had amyloid disease. I am not given any report of a Congo red test, so I assume it was normal if done or that it was not done. Amyloid in the liver usually does not cause jaundice or this much fever.

Did this patient have tuberculosis? There was no sign of tuberculosis elsewhere, although he had a family history of tuberculosis. Tuberculosis of the liver itself is very rare; I merely mention it as a possibility, but believe the evidence for other conditions seems to be more striking than that for tuberculosis. Malignancy? Yes; the patient may have had diffuse malignancy involving the bone marrow. He may have had metastatic disease to the liver. Once in a while, when a large liver is due to metastatic disease, a large spleen results. That is not common. I would expect that if he had enough malignancy to produce the rest of the picture it should have been easily identified — that is, if it was carcinoma, sarcoma or anything like that. That just about leaves me with another type of malignancy — very often the catch basket for everything when we do not know the answer — that is, lymphoma.

Will you show us the x-ray films, Dr. McCort? I assume there were no lesions in the bones other than those of the ribs.

DR. JAMES J. MCCORT: The examination of the chest shows the changes described in the protocol: the deformities in the lower ribs due to the previous operation, the adhesion in the costophrenic sinuses and the somewhat high position of the diaphragm. The lungs are clear and the intrathoracic lymph nodes do not seem to be enlarged. In the examination of the abdomen, with the film centered over the liver and spleen, the edge of the spleen comes below the costal margin and may be slightly enlarged. The edge of the liver is well below the costal margin and is moderately enlarged.

DR. ELLIS: Below the iliac crest?

DR. MCCORT: One edge is projected below it. We cannot see the kidneys and the upper margin of the right psoas shadow is not well defined. The obscuration may be due to tumor or to the large liver. There is also a suggestion in the abdominal film of increased intraperitoneal fluid.

No evidence of any lesion in the bones of the lumbar spine, pelvis or thoracic cage is noted.

DR. ELLIS: No barium studies were done?

DR. MCCORT: The patient had only a barium swallow at the time of the chest examination to exclude the possibility of varices or periesophageal lymph-node enlargement. The examination was carried no further.

DR. ADAMS: The man was too sick for any barium studies.

DR. ELLIS: I think the x-ray films show an enlarged liver. Moreover, he must have had liver disease to account for the jaundice and the hepatomegaly. Could it have been cirrhosis? As I recall, there was no mention of a bromsulfalein-retention test. The cephalin-flocculation test was negative. The alkaline phosphatase does not give me any help. The albumin-globulin ratio was normal and the total protein was low, which I think is perfectly consistent with infection or any other systemic disease and not necessarily due to primary liver disease. The prothrombin time was only slightly prolonged. I am tempted then to assume that a diagnosis was made by liver biopsy. That assumption may be false because Dr. Castleman may have had a chance to examine the patient shortly after the liver biopsy and may have made the diagnosis then. I do not believe the patient had primary parenchymal liver disease. I think malignant lymphoma of some type would explain the fever, the leukopenia and the bleeding tendency. I assume that he had a bleeding tendency for two reasons: he had hemorrhagic spots on the skin with a skin rash and Dr. Adams assured me that the rectal mass was a figment of somebody's imagination, so if he was passing clots of blood by rectum then perhaps he was bleeding diffusely from the rectal mucosa — trauma of the rectal examination added support to this. Why was he jaundiced if he had lymphoma? The jaundice may have been due to large lymphomatous nodes in the region of the porta hepatis, but there was nothing to suggest obstructive jaundice in this patient. Then perhaps there was enough diffuse involvement in the liver to cause damage of liver cells or enough congestion of liver cells and bile canaliculi to cause jaundice.

I am going to say that the patient had lymphoma of some kind. I have no way of knowing whether it

was Hodgkin's lymphoma, lymphosarcoma, reticulum-cell sarcoma or giant-follicle lymphoma. I would think he had no recurrence of the chronic sepsis. I do not believe he had pylephlebitis of the liver.

Dr. Alfred Kranes: I was muttering under my breath that a similar patient I had a short while ago died and showed miliary tuberculosis. I do not see how that diagnosis can be made clinically. Dr. Ellis considered it and excluded it.

Dr. Earle M. Chapman: I am very intrigued that a man forty years old came in with fever and all that was said about his occupation was that he was a wool worker. What did he do?

Dr. Adams: The patient was repeatedly quizzed about the details of his job. The best we could learn was that he worked in a factory where dyed cloth was processed in some way. He was a supervisor and had no contact with any of the material.

Dr. Chapman: If volatile substances had been used he may have been exposed. They may have used azo dyes that were volatile, or benzol or benzol products. I think that some kind of intoxication has to be considered.

Dr. Ellis: You have no evidence from the tests that he had any real liver damage.

Dr. Chapman: I do not think we know what the man was exposed to. There is the possibility of an occupational disease.

Dr. Benjamin Castleman: Would that cause fever for such a long period of time?

Dr. Chapman: If it produced agranulocytosis, it would.

Clinical Diagnosis

?Lymphoma.
?Miliary tuberculosis.

Dr. Ellis's Diagnosis

Malignant lymphoma involving liver.

Anatomical Diagnosis

Malignant lymphoma, Hodgkin's type, involving liver.

Pathological Discussion

Dr. Castleman: The operation on this patient was an aspiration liver biopsy. This was one of the few cases on which we have been able to make a diagnosis of lymphoma of the liver. There was a variability of cells quite characteristic of the Hodgkin variety of lymphoma and it certainly fits in with the fever that he had. In the small aspiration biopsy there were numerous foci of Hodgkin's disease — 2 or 3 foci in each field — so it was a diffuse disease. There was also enough bile stasis in the liver parenchyma to suggest that the nodes in the porta hepatis may have been involved and have been a factor in obstructing the flow of bile.

Dr. Adams, would you summarize the opinion on the ward?

Dr. Adams: I want to congratulate Dr. Ellis on his discussion. On the ward we pursued the same line of reasoning. Sepsis appeared to be excluded by the white-cell count. Either lymphoma, aleukemic leukemia or miliary tuberculosis seemed most likely. The bone marrow excluded leukemia. We did not do a lymph-node biopsy because we could not be sure that the lymph-node enlargement was not a part of the penicillin reaction. That turned out to be a good judgment; as the patient recovered from the eruption, the lymph nodes returned to normal size. He was given ACTH (adrenocorticotrophic hormone) and cortisone at the suggestion of Dr. Jacobson with the thought in mind that, because of the danger of bleeding, we had best not have a liver biopsy performed unless we could raise the platelet count. These drugs did raise the platelets. We did not consider amyloidosis.

We thought the skin eruption was a response to penicillin. Somewhat later in the disease penicillin was ordered by someone not familiar with the past history. The patient received it for several days before I learned about it. He had no more trouble, so one now wonders if the reaction was not due to one of the other antibiotics administered before admission here. This man was almost dead when we did the biopsy; his white-cell count was down to about 800 or 900. In spite of the risk we decided that the one thing we could do was treat him with x-ray — something possibly to be gained; nothing to lose. He has had about 1100 r and has improved a great deal. How long the improvement will last one cannot predict. When the x-ray course was completed he was transferred back to his hometown hospital. He must have had some liver damage in addition to biliary obstruction because when he was in the other hospital he had double daily rises in temperature.

With this blood picture, and the enlarged liver and spleen if I had seen him as a soldier returning from the Mediterranean area I would have included kala-azar as one of the likely diagnostic possibilities. He was a "dead ringer" for several cases of this disease that I encountered during the war.

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DELETERIOUS EFFECT OF ACTH AND CORTISONE ON TUBERCULOSIS

THE marvels of ACTH and cortisone have now been trumpeted the world over — in the medical and lay press and in extensive and aggressive advertising campaigns carried out by the manufacturers of these products. As might be expected with such new agents when they produce striking effects in conditions in which there previously were no very effective remedies, the apparently beneficial results have been extolled and often exaggerated and the ill effects and possible dangers have usually been minimized. Such publicity has undoubtedly led to excessive and unwarranted uses of these hormones by many physicians who prescribe them not for well established indications but for conditions that they are unable to diagnose or in which the results of other therapy are considered unsatisfactory. Often these agents are given only because of pressure from the patients or their friends and relatives.

In many situations, just as in cases in which antibiotics are needlessly or carelessly prescribed, there is an unfortunate tendency to avoid or delay carrying out essential diagnostic procedures until the results of the tests are modified by the effects of the agents that have been administered. Moreover, little or inadequate attention is focused on the possible harm that might result from the therapy, and the potential dangers are not properly weighed against the possible or illusory benefits that may accrue from the treatment.

Attention has previously been called in these columns[1] to the many reports of the use of ACTH and cortisone in experimental infections, almost all of which have shown that these agents have no beneficial effects on the course and outcome of the infections and indeed more often aggravate them and sometimes even render them less susceptible to treatment with antimicrobial agents. In addition, the laboratory investigations have indicated that these hormones sometimes change relatively innocuous infections into severe and even fatal ones.*

Because of these reports and because of some suggestive clinical evidence of deleterious effects of the use of these preparations in patients with tuberculosis, the National Tuberculosis Association[2] several months ago recommended that ACTH and cortisone be not used in patients with active tuberculosis and that they be used with extreme caution in patients with possibly latent tuberculosis until further investigation has shown that such administration may be safe. It was urged that diagnostic examinations for tuberculosis be carried out in all patients treated with these substances.

More recently, the chairman of the Committee on Therapy of the American Trudeau Society has requested the medical profession to co-operate in a survey of possible beneficial or deleterious effects

*The most recent example[3] is the demonstration that adult mice, which are not ordinarily susceptible, may be lethally infected by the Coxsackie virus if cortisone is given first.

of cortisone and ACTH on tuberculous infection in man.[4] It is desired to gather reports of the use of these agents in both pulmonary and extrapulmonary tuberculosis, including patients with known active tuberculosis in whom there is no apparent benefit, those in whom there is exacerbation of clinically active or inactive tuberculosis during treatment and those in whom an apparently favorable effect of the hormones is observed. Such information should be most helpful in determining more precisely the relative benefits and dangers involved and perhaps in helping to delineate the proper indications or contraindications for their use under these conditions.

Meanwhile reports are already trickling in, perhaps in anticipation of these warnings or as a result of them. Last winter, at the Veterans Administration's Tenth Conference on the Chemotherapy of Tuberculosis,[5] many laboratory observations on the aggravation of experimental tuberculous infections in animals by ACTH and cortisone were reviewed and at least one report of a clinical counterpart was presented. One of the participants in the conference,[6] however, was not convinced that harmful effects from ACTH and cortisone had been conclusively demonstrated in human tuberculous infections.

At about the same time, Whorton and his coworkers[7] reported to the Southern Society for Clinical Research their findings in a group of patients who received cortisone for a variety of diseases and who either developed infections while under therapy or had a rapid spread of pre-existing, otherwise benign lesions while receiving the hormone. Included in their series were two patients who showed extensive tuberculosis at autopsy although little evidence for it existed during life; other patients with spreading superficial infections that usually are well localized; and one patient with pneumococcal pneumonia discovered at post-mortem examination but unrecognized during life. These workers stressed the point that enhancement of bacterial infections can be a treacherous side-effect of cortisone therapy and must be constantly kept in mind while this substance is being administered.

A recent issue of the *Journal of the American Medical Association* carried three papers each of which reported the rapid appearance or progression of pulmonary lesions resulting from the treatment of a patient with ACTH or cortisone for rheumatoid arthritis. In the first of these patients,[8] a roentgenogram taken three months before cortisone therapy was started showed normal lungs. The cortisone was given intermittently over a period of seven months. Toward the end of this time a moderately extensive infiltration was demonstrated by x-ray at the base of one lung; this rapidly progressed to involve that entire lung with marked cavitary disease, and the patient died. Unfortunately, the exact nature and etiology of this pulmonary lesion was not determined, but it was considered on clinical and roentgenographic evidence to be tuberculous.

The second patient[9] had what was considered old and arrested pulmonary tuberculosis when cortisone therapy for rheumatoid arthritis was started. The lesion in the lung had shown no change by x-ray during more than three years, and tubercle bacilli had at no time been demonstrated in the sputum. Two months after therapy was started and while the patient's general condition and her arthritis were apparently progressing favorably, she had a large hemoptysis. An x-ray film of the chest at that time showed cavitation in the lung, and tubercle bacilli were demonstrated in the sputum for the first time in four to five years of observation.

The third patient[10] was found to have no abnormality of the lung in an x-ray film taken at the beginning of ACTH therapy and suddenly manifested clinical evidence of pulmonary tuberculosis during therapy with this agent and cortisone. Repeated sputum examinations in this case revealed many tubercle bacilli. At the time of the report, the patient was showing a poor response to treatment with streptomycin and para-aminosalicylic acid.*

Although these cases may represent only rare and isolated examples among the host of patients who have received ACTH and cortisone for a number of conditions, it is very likely that many other similar cases have occurred and either have gone

*Still another case[11] has recently been reported in which extreme miliary tuberculosis was found at autopsy after two courses of cortisone therapy, one of thirty days and the other of seventeen days. The patient died about three months after the cortisone was started, but the possibility could not be excluded that miliary tuberculosis was already present at that time.

unrecognized or have not been reported. It is hoped that some indication of the frequency of such occurrences will be obtained from the efforts of physicians collaborating with the American Trudeau Society. In the meantime it will be well for physicians to use great discretion in prescribing these agents. Furthermore, although the use of suitable antibiotics for the treatment of pre-existing infections or for those arising during hormone therapy is obviously indicated, such use of antibiotics should certainly not be considered justification for the promiscuous and indiscriminate use of ACTH and cortisone.

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MEETING OF THE COUNCIL

Nearly 300 of the 386 members were present at the regular meeting of the Council of the Massachusetts Medical Society on October 3. The usual attendance is 150 to 160. This excellent turnout may be accounted for, in part, by the fact that an excellent luncheon was served in the new and almost virginally spic-and-span Society headquarters at 22 Fenway, which many councilors were visiting for the first time.

A rising vote of thanks was given the Society Headquarters Committee for their share of responsibility in the provision and maintenance of the new permanent home.

The Secretary of the Society again expressed his perennial hope that some action will be taken in favor of periodic registration of the physicians of this Commonwealth. He was supported by the President, and the matter was referred to the Committee on State Legislation.

The report of the Committee on Public Relations was accepted, with the exception of an amendment providing for the "implementation" of the recommendation by Dr. Maraldi's subcommittee on Emergency Medical Care that a telephone service be maintained by the Society or by the Suffolk, Norfolk and Middlesex South district societies, whose members are chiefly responsible for emergency care of patients in the Boston area. The general opinion seemed to be that although emergency medical care is of great concern to the State Society the problem of providing it must be solved at the local level. Furthermore, excellent progress is being made by the various district societies toward the solution of this problem.

The action of the Executive Committee in voting approval of the National Fund for Medical Education and recommending that physicians contribute to it either directly or through the American Medical Association was supported, and a suggestion by Dr. Hagler of Hampden that the Society contribute annually a sum of money to this fund, — the amount to be included in the annual budget after consultation with the officers of the Society, — was referred to the Committee on Finance.

The Committee on Arrangements reported that the annual meeting will be held at the Hotel Statler May 20–22, 1952.

On recommendation of the Nominating Committee it was voted that Dr. Joseph Garland, Editor of the *New England Journal of Medicine*, be named annual orator to replace the late Dr. John Fallon.

A suggestion that the annual dues of $35 are too high, and that a slight annual deficit might have a more salutary effect on free spending than provision for a surplus each year, was referred to the Committee on Finance.

The business of the Council was conducted *tuto, cito et jucunde*, from its prompt call to order at 10:30 until the ingestion of the last bit of ice cream and cake. For this, credit goes to the efficient President and Secretary.

"OF THAT FEATHER"

"I am not of that feather to shake off
my friend when he must need me."
— Shakespeare

FEW have more friends than the physician. As much as anyone he is accorded that combination of affection and respect that, being freely bestowed, is the essence of friendship. Friendship and science are his two most precious possessions, and the friends are not all of one trade, class, race, religion or financial status. Many of them he knows intimately, others perhaps only by hearsay.

George VI of England was not the only person revealed to have a friend when eight-year-old Jill Stebbings wrote him: "Daddy tells me that Mr. Price Thomas is one of your doctors, so I am writing to tell you, as I had a serious lung operation done by him and now I am very fit and well, he is a very kind and clever man." Mr. Price Thomas is clearly not of that feather to shake off his friends when they must need him. Mr. Price Thomas, as a true physician, is kind even before he is clever.

As it is manifestly impossible for Jill's father to defray the cost of her illness with as little financial sacrifice as the King, the government comes to her aid. However, in the United States of America it is still squarely up to the citizen, rather than to his government, to undertake the responsibilities of the good Samaritan, who in this complex age more often appears as an agency than as a solitary wayfarer.

So it is that in 1951 the Red Feather symbolizes to the physician not only *caritas* and *amicitia* but a bold conception of voluntary medical care and organization that has no relation to the Welfare State. To quote from "Facts for Volunteer Workers," it symbolizes "the organization which coordinates the services and budgets the funds for the 300 Red Feather services of your Metropolitan Boston community in the fields of: Children, Hospitals, Youth Services, Health Services, Family Services, Neighborhood Houses, Services to the Armed Forces, Handicapped, Care for Aging."

In the 1948–1949 drive, 1127 (63.4 per cent) of the 1778 physicians of Metropolitan Boston made gifts to the United Community Service Organization. Of these contributors, 55 per cent gave $25 or more; 33 per cent gave $30 or more; and nearly 20 per cent gave $100 or more. These distributions were published last year in the *Journal* to provide a scale against which each physician might be enabled to answer that question, "What should I give?" Whether such statistics do or do not provide a useful frame of reference is difficult to assess. However that may be, the fact is that in last year's campaign physicians gave 19 per cent more than in 1948–1949.

Messrs. Lindsay & Blakiston, of Philadelphia, have published a curiously-contrived book for the pocket, which every practitioner who sees it will want. . . . The title is "The Physician's Visiting List, Diary and Book of Engagements, for 1852."

Boston M. & S. J., *October 29, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

EHRENFRIED — Albert Ehrenfried, M.D., of Brookline, died on September 26. He was in his seventy-second year.

Dr. Ehrenfried received his degree from Harvard Medical School in 1905. He was a fellow of the American Medical Association and a member of the American College of Surgeons.

A son and two daughters survive.

MEREDITH — Florence L. Meredith, M.D., of Watertown, died on August 16. She was in her sixty-fourth year.

Dr. Meredith received her degree from Tufts College Medical School in 1916. She was professor of hygiene at Tufts and Jackson colleges for many years. She was a member of the American Public Health Association, the Association of Women in Public Health, the National Committee for Mental Hygiene, the American Psychiatric Association, the American Association for the Advancement of Science and a fellow of the American Medical Association.

ROWE — Leonard B. Rowe, M.D., of Natick, died on September 19. He was in his seventy-eighth year.

Dr. Rowe received his degree from the University of Vermont College of Medicine in 1906. He was an organizer and member of the staff of the Leonard Morse Hospital and formerly on the staffs of the Framingham Union and Newton-Wellesley hospitals. He was a fellow of the American Medical Association.

His widow and two sons survive.

WILCOX — DeWitt G. Wilcox, M.D., of Newton, died on September 26. He was in his ninety-fourth year.

Dr. Wilcox received his degree from Cleveland University of Medicine and Surgery in 1908. He was professor of gynecology, emeritus, at Boston University School of Medicine. He was a fellow of the American College of Surgeons and a member of the Newton Medical Club.

A son and two daughters survive.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATHS

CHESLEY — Harry O. Chesley, M.D., of Rollinsford, died on August 5. He was in his eightieth year.

Dr. Chesley received his degree from Dartmouth Medical School in 1898. He was a past president of the New Hampshire Medical Society and the New Hampshire Surgical Club.

His widow and a sister survive.

TOGUS — Leopold T. Togus, M.D., of Manchester, died on July 14. He was born in Bluffton, Minnesota, on November 6, 1880, the son of Theodore and Frances (Simmons) Togus, and attended the Tilton School and Manchester High School, later graduating from Boston University in 1903. After his graduation from the University of Vermont College of Medicine in 1909 he practiced general medicine in Hooksett from 1910 to 1917. In 1920, after further study at the Manhattan Eye, Ear and Throat Hospital, he began practice in Manchester, specializing in diseases of eye, ear, nose and throat. He was the attending specialist at Elliott Hospital from 1922 until his retirement in 1949.

He was a captain in the Medical Corps of the United States Army from 1917 to 1919 and a major in the Medical Reserve Corps from 1921 to 1931. Dr. Togus was also a public-spirited citizen, as is shown by his membership on the Hooksett School Board from 1910 to 1917 and on the Hooksett Public Library's board of trustees. He was a member of the American Medical Association, the New England Oto-Laryngological Society, the New Hampshire State Medical Society, the Hillsborough County Medical Society and the New Hampshire Surgical Club. He was a fellow of the American Academy of Ophthalmology and Otolaryngology and a member of Jewell Lodge, F. & A. M., Suncook; the Freeport Consistory 32nd, Freeport, Illinois; Post 79, American Legion; and the Ragged Mountain Fish and Game Club of Andover. He was a member of the Grace Episcopal Church.

He is survived by his widow, Mary M. (Wilcox) Togus; one daughter, Frances Mary Togus; a sister, Mrs. William Cowan of Brooklyn, New York; a nephew; and two nieces.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

ALABAMA ACCEPTS MASSACHUSETTS PREMARITAL CERTIFICATE

The state of Alabama has notified us that it will accept the Massachusetts premarital-examination certificate, if signed by a Massachusetts physician, and the blood test for syphilis, if performed at Massachusetts's State Wassermann Laboratory.

It is therefore suggested that Massachusetts physicians add Alabama to the list of those states accepting the Massachusetts premarital-examination certificate (*New Eng. J. Med.* **244**:194-196, 1951).

Since the publication of this list the following additional states have agreed to accept the Massachusetts premarital-examination certificate: Alabama, Georgia, South Dakota and the Territory of Hawaii.

IMPROVING THE SEROLOGIC TEST FOR SYPHILIS

After November 1, 1951, the Wassermann Laboratory of the Institute of Laboratories plans to use cardiolipin and lecithin instead of extract of beef heart in the preparation of its indicator (antigen) for the Hinton test. This change is being made because the test when so modified increases the percentage of positive reactions in syphilitic persons without increasing the percentage of positives in nonsyphilitic subjects. This statement is based on the results of the last three evaluations of serologic tests conducted by the United States Public Health Service and on the testing of 46,000 blood specimens by the American Red Cross Center in Boston. In this latter group only 49 tests were found to be positive, which is less than 1 positive in 900 presumably healthy persons. The increased accuracy of the test not only will aid greatly in the detection of syphilis but will be valuable in excluding the diagnosis in persons who give no history of the infection but show suggestive signs or symptoms of it.

JOHANNES IPSEN, JR., M.D.
Institute of Laboratories

CORRESPONDENCE

CORRECTING FOR SMALL NUMBERS

To the Editor: The August ninth number of the *Journal* contains an editorial entitled "Anatuberculin Vaccination" that interests me because of what appear to be unwarranted conclusions in the last paragraph, which reads: "The epidemic had brought about an unintentional but quite conclusive experiment, which indicates the efficacy of Petragnini's anatuberculin in protecting infants against tuberculosis . . ." If one applies one of the commonly used tests of significance to the figures given, it can be demonstrated that the difference of 10 per cent between the incidence of tuberculosis in the inoculated and the control groups could occur nearly 20 times out of a hundred as a result of chance alone in groups as small as those considered. If we use the standard error of the difference between two proportions, sigma is 7.4 and $\frac{X}{\text{sigma}}$ is 1.35; p is then approximately 0 19.

This means that the 10 per cent difference in morbidity rates between treated and untreated groups could have occurred 19 times out of 100 as a result of chance alone, entirely unrelated to treatment. As a check I applied the X^2 test and obtained 2.08, which makes $p = 0.16$. This means that, by this test of significance, such a difference could have resulted from chance alone in 16 out of 100 instances with groups of this size. An event that could occur as often as 5 times out of 100 as a result of chance alone is not considered statistically significant. A safer and more rigid standard is that of 1:100. How, then, can one conclude that this is a "conclusive experiment" indicating the efficacy of the inoculation in protecting against tuberculosis? It is true that if one applies one of the tests of significance to the mortality rate, the difference is significant, as $\frac{X}{\text{sigma}}$ is here about 3. This means that the 14 per cent difference in mortality rates between the two groups could occur as a result of chance alone only about once in 400. The concluding paragraph, however, was referring to infection with tuberculosis and not death from tuberculosis.

Having always experienced great difficulty with even simple arithmetic, I am naturally reluctant to raise such a point, which will undoubtedly result in my humiliation. No doubt there is an adequate explanation for the conclusions,

which impressed me as unfounded. I should appreciate being enlightened.

ALLEN S. JOHNSON, M.D.

Springfield, Massachusetts

Note: Dr. Johnson's letter was submitted to a kindred spirit, who also has trouble with arithmetic and admits to having to use an electric calculator. The machine showed that Dr. Johnson is quite correct in saying that the difference in tuberculous morbidity between the two groups may readily have occurred by chance — and that the difference in tuberculous mortality is unlikely to have occurred by chance. The chances are about 1 in 400, or 1 in 100 (if Yates's correction for small numbers is used) against the inoculated group's having no deaths by luck alone. (The editor would appreciate being given such odds against filling an inside straight.) Dr. Johnson's points are in general well taken and expressed in a manner satisfactory to the electronic robot. He would have been allowed the last word had it not been that, considered together, the two favorable differences are quite impressive and justify further investigation of the efficacy of Petragnini's anatuberculin as a protective measure against tuberculosis. — ED.

BOOK REVIEWS

Surgery: Orthodox and heterodox. By Sir William Ogilvie, K.B.E., D.M., M.Ch., F.R.C.S. 8°, cloth, 241 pp., with 30 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $4.00.

It is a pleasing task to review this book by Sir Heneage Ogilvie, not only because it is so interesting and so full of valuable observations but also because the reviewer has been privileged to know the author intimately over the years and to have seen him frequently here and in London. In a book of this character, made up almost entirely of a philosophic approach to the subject of surgery, who writes it, what is his background of experience, what is his character and what is the quality of his judgment are of great importance. Heneage Ogilvie is a man of wide and versatile experience, — in war, in peace and in his own country and its possessions, — and one who is very familiar with surgery in the United States, Canada and continental Europe.

Unlike so many writers who feel competent to sit at home in judgment of distant centers, Sir Heneage has, over the years, been in almost constant motion. More than once I have looked up over my shoulder, when operating, and seen him unexpectedly or have recognized his voice among observers. Sir Heneage is almost as well known at meetings of the medical and surgical societies in this country as he is at home. This makes him particularly qualified to write a book of this character.

The book is filled with gems of truth, such as "true education is arranged experience" and "The surgeon is sometimes despised by the intelligentsia of medicine as a mechanical craftsman. But though he be a hewer of wood and a drawer of water, he has the assurance that such services are useful to mankind. . .Surgery may not require brains or bring a fortune, but it is the best job in the world."

Under "The American Surgeon," taken from the final pages of a diary kept during a visit to America in 1937 and published in the *Guy's Hospital Gazette*, is a comment that will interest many Americans; that is on the Halsted tradition. Under this is an interesting comment revealing the capacity for expression in this attractive book. "Halsted was one of the giants of the last generation and, like many great men, he left behind him admirers rather than followers, much in the same way as MacEwen sterilized the surgery of Glasgow for a generation. Where these men worked one finds a tendency to treat their 'footprints on the sands of time' as shellholes to be defended against all comers and re-excavated when they crumble, rather than as an indication of the direction in which they were travelling, of the path they were tracing when they fell; one to be followed to its end or as near it as each explorer can get, leaving the actual prints to be filled in as the sands are trampled round them by the eager throng."

Under a separate heading Sir Heneage makes a comment that reveals the keenness of his observation. He says: "I never saw Halsted, but technique that is so identical in several cities must be his own." Those of us who have grown up in America are keenly aware of the fact that probably no man ever was more reverenced by his pupils than Halsted or put his mark more definitely on both the surgery of his times and the men whom he trained. When a surgeon can leave his imprint on almost every field of the surgery of his time and when a teacher can so impress his pupils that they reverently speak of him long after he is dead as "the old Professor," he must indeed have possessed remarkable qualities — and this, as Sir Heneage says, in spite of a shy and retiring personality.

Some of these quotations are included merely to encourage those who are interested in the philosophic side of surgery to give themselves the pleasure of perusing this not only valuable but very readable volume. It is a veritable treasure chest of sound surgical philosophy.

Under "Religio Chirurgi" is a paragraph well worth quoting: "The perfect job in life is one which offers steady employment while the faculties remain active, reasonable remuneration, a succession of tasks sufficiently varied to demand constant care and provide constant interest, freedom from dictation or interference, and a knowledge that the work is necessary and beneficial. Most branches of medicine satisfy some of these demands, but few, other than surgery, satisfy all."

There is a real inclination on the part of the reviewer to quote from this small volume to an unwise extent and so deny the real pleasure that will come to the surgeon who wishes to spend a happy and stimulating evening with it.

FRANK H. LAHEY, M.D.

Natural Childbirth: A manual for expectant parents. By Frederick W. Goodrich, Jr., M.D. 8°, cloth, 175 pp., with illustrations. New York: Prentice-Hall, Incorporated, $2.95.

This is another of the already considerable number of books, by various authors, that have appeared in sequence to Grantly Read's original volume, "Childbirth Without Fear." The concept that he there proposed has been advanced, expanded and modified by successive writers, but it is essentially sound and remains fundamentally the same.

The first printing of the present excellent work was favorably reviewed in the *Journal* at the time of its publication. This second printing, within a year of the first, is well illustrated, with 16 pages of admirable drawings and engravings. The book is intended primarily for prospective parents but may well be read and taken to heart by every American obstetrician. We are certain that Dr. Read himself, Dr. Goodrich and all others who have written on this subject would be unanimous in giving credit to no one individual as the "originator of natural childbirth" but to Nature herself, who seldom errs, whereas we often do.

ROBERT M. GREEN, M.D.

The American Illustrated Medical Dictionary: A complete dictionary of the terms used in medicine, surgery, dentistry, pharmacy, chemistry, nursing, veterinary science, biology and medical biography with their pronunciation, derivation and definition. Edited by W. A. Newman Dorland, M.D., Lieutenant-Colonel, M. R. C., United States Army. 8°, cloth, 1736 pp., with 720 illustrations and 48 plates. Twenty-second edition. Philadelphia: W. B. Saunders Company, 1951. $10.00.

The previous edition of this standard medical dictionary was published in 1947; for this semicentennial edition new design and new typography have been used. The text has been brought up to date and many unnecessary cross-references have been eliminated. New features include an article on the fundamentals of medical etymology by Professor Lloyd W. Daly of the University of Pennsylvania and a table of modern drugs and dosage compiled by Dr. Austin Smith, editor of the *Journal of the American Medical Association.*

"Dorland's" dictionary continues to live up to its unsurpassed reputation as an essential reference work. It should be in all medical and public libraries and is recommended to physicians, scientists and other interested persons.

JAMES F. BALLARD

Your Weight and Your Life: A scientific guide to weight reduction and control. By Alfred L. George, M.D. 8°, cloth. 272 pp., with tables. New York: W. W. Norton and Company, Incorporated, 1951. $2.95.

Dr. George has written a sound, common-sense book for overweight persons. It also contains much practical information on metabolism and nutrition. The popular misconceptions concerning the causes of obesity, — glandular, heredi-

tary, temperamental and metabolic, — are exposed, and it is shown how family eating habits, attitudes and emotional disturbances lead to overeating. Although overweight may be reduced by sensible dietary measures it is pointed out that dietary treatment cannot be spasmodic but must be maintained when a normal weight has been reached. There are a number of valuable tables: the basic reduction diet with permissible substitutes and their caloric values and detailed instructions for persons on a reduction program; and the 1000-, 1200- and 1500-calorie diets calculated for a week. The text is concluded with a list of common foods and their caloric content, and a list of good sources of important minerals and vitamins. The printing is well done, and there is a good index. The book is recommended for all medical and public libraries.

JAMES F. BALLARD

Cerebral Angiography. By P. Almeida Lima. With an introduction by Egas Moniz. With a foreword by Sir Hugh Cairns, K.B.E., D.M., F.R.C.S. 8°, cloth, 221 pp., with 181 illustrations. New York: Oxford University Press, 1950. $8.75. (Oxford Medical Publications.)

In 1926 Egas Moniz, who later was awarded the Nobel prize, demonstrated for the first time, by means of an induction into the carotid artery of an opaque substance, the arterial and venous circulation of the brain, and after about five years the technic of induction was standardized with thorotrast as a contrast medium. This method now has become a standard neurologic procedure, particularly valuable in visualizing intracranial tumors, cerebral aneurysms and malformation of the blood vessels. One of the early investigators was Almeida Lima, head of the neurologic department of the Hospital Julio de Matos in Lisbon, who has worked with Egas Moniz from the beginning on cerebral angiography. The present book summarizes the results of this research, with excellent pictures of the roentgen-rays and a full account of the methods employed in the demonstration of intracranial lesions. The book is finely printed and contains a satisfactory index and references to the pertinent literature.

HENRY R. VIETS, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Cirrosis Hepaticas. By Profesor Diaz Rubio and others. Ponencias de la III reunión de la Sociedad Española de Patología Digestiva y de la Nutrición. 8°, paper, 313 pp., with illustrations. Madrid: Diana, Artes Gráficas, 1949.

These important proceedings are devoted to a discussion by six physicians on various aspects of cirrhosis of the liver. The topics include experimental cirrhosis, pathologic anatomy, early diagnosis, cirrhosis with splenomegaly, pathology of the liver in children and its relation to cirrhosis and pathogenesis and treatment. Each of the papers is documented with a list of references. The paper by Professor Diaz Rubio on pathogenesis and treatment comprises a monograph in itself. The illustrations are excellent, and the book is well published. It is recommended for all reference collections on diseases of the liver.

Recent Advances in Nutrition: With particular reference to protein metabolism. By Paul R. Cannon, Ph.D., M.D., chairman of the department of pathology, University of Chicago. In collaboration with others. 8°, cloth, 74 pp., with 23 illustrations. Lawrence, Kansas: University of Kansas Press, 1950. $2.00. Porter Lectures, Series 14.

This small book presents three lectures delivered to the students and faculty of the University of Kansas. They are concerned with recent progress in nutrition, dietary essentials in relation to tissue-protein synthesis and pathologic aspects of protein nutrition and their relation to amino-acid utilization. A bibliography of references to the recent literature is appended to the text.

Histamine Antagonists. By Frederick Leonard and Charles P. Huttrer, Warner Institute of Therapeutic Research, New York City, New York. 8°, paper, 122 pp., with 48 illustrations. Washington, D. C.: Chemical-Biological Co-ordination Center, National Research Council, 1950. $1.50. Review No. 3.

This monograph is devoted principally to the chemistry and pharmacology of the histamine antagonists. There is a special section on structure-activity relations with 71 pages of activity tables. There is a bibliography of 224 references. An index to the text would have made the monograph more valuable for reference purposes. It should be in all collections on the subject.

Carcinoma of the Breast. By C. D. Haagensen, M.D., Institute for Cancer Research and Columbia University College of Physicians and Surgeons. 8°, paper, 120 pp., with 56 illustrations. New York: American Cancer Society, Inc., 1950. Fifth of a series on Early Recognition of Cancer.

This monograph is well written and well illustrated, and is divided into two parts, on diagnosis and treatment, including radiation, surgery and palliation by radiotherapy and hormones. The publishing is excellent. The type used is large and makes for easy and comfortable reading. The monograph should be in all collections on cancer and available to all practicing physicians. Early diagnosis is essential for the successful treatment of mammary cancer.

The Transmission of Nerve Impulses at Neuroeffector Junctions and Peripheral Synapses. By Arturo Rosenblueth, head of the department of physiology and pharmacology of the Instituto Nacional de Cardiología de Mexico. 8°, cloth, 325 pp., with 98 illustrations. Cambridge, Massachusetts: The Technology Press, and New York: John Wiley and Sons, Inc., 1950. $6.00.

This monograph presents in systematic form the knowledge of chemical transmission at the junctions of the motor nerves with striated muscles and at the synapses in autonomic ganglia. There is a bibliography of 720 references and indexes of authors and subjects. The publishing is excellent and the book should be in all collections on the physiology of the nervous system.

Toxaemias of Pregnancy, Human and Veterinary: A Ciba Foundation Symposium. Edited by John Hammond, M.A., D.Sc., F.R.S., F. J. Browne, M.D., D.Sc., F.R.C.S., and G. E. W. Wolstenholme, O.B.E., M.B. 8°, cloth, 280 pp., with 93 illustrations. Philadelphia: The Blakiston Company, 1950. $4.50.

This composite volume reports the proceedings of a symposium held in January, 1950, at which twenty-nine experts in their particular fields read papers on the various aspects of the so-called toxemia of pregnancy. Seven of the papers are on veterinary aspects; the other twenty-two deal with human beings or are of a general character. The papers are short and, where necessary, documented with lists of selected references. The printing was done in Great Britain, and the publishing is excellent. The book should be in collections on obstetrics and on veterinary medicine.

NOTICES

ANNOUNCEMENT

Dr. Lester J. Honig, formerly of Pittsfield, announces the opening of an office for the practice of internal medicine and gastroenterology at 880 Fifth Avenue, New York City.

MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

The fall meeting of the Massachusetts Society of Examining Physicians will be held at the Harvard Club on Wednesday, October 31. Dinner will be served at 6:30 p.m. Dr. Edward A. Edwards, associate professor of anatomy at Harvard Medical School and associate on the surgical staff of the Peter Bent Brigham Hospital, will speak on "The Clinical Picture of Severe Frostbite," and Dr. Fredrick J. Stare, professor of nutrition at the Harvard School of Public Health, will speak on "Studies of the Intravenous Use of Emulsion Vitamin K in Controlling Toxicity Due to Dicumarol."

SUFFOLK DISTRICT MEDICAL SOCIETY

The Suffolk District Medical Society will hold an all-day clinical meeting on Wednesday, January 23, 1952, at the Massachusetts General Hospital. Details of the program will be announced later.

DIABETES FAIR

The New England Diabetes Association will hold a "Diabetes Fair" on November 14 and 15, from 11:00 a.m. to 10.00 p.m., at Horticultural Hall, Boston, in connection with National Diabetes Week.

An informative program of interest to the public, social-service workers, dietitians, medical students and physicians has been arranged.

A variety of exhibits concerning diabetes and its treatment will be shown, consisting of displays on medical and surgical aspects, dietetics, pharmaceuticals, books, literature, social-service aids, insurance, camps, education and employment. Urine and blood-sugar testing facilities will be available.

On Wednesday evening, November 14, at 8:00 p.m., a symposium on diabetes will be held at Horticultural Hall. Dr. Frank N. Allan will preside. The speakers will be Dr. Harry Blotner, Dr. Frederick W. Williams, Dr. F. Gorham Brigham and Dr. Elliott P. Joslin.

THE NEW ENGLAND CARDIOVASCULAR SOCIETY

The next meeting of the New England Cardiovascular Society will be presented by the Massachusetts General Hospital and the Boston City Hospital on Thursday, November 8, at 8:00 p.m. at the Dorothy Quincy Suite of John Hancock Hall, 180 Berkeley Street, Boston.

PROGRAM

MASSACHUSETTS GENERAL HOSPITAL — Dr. Edward F. Bland presiding

1. Essential Xanthomatosis, Coronary Heart Disease and Hypercholesterolemia. Drs. Edwin O. Wheeler, Howard B. Sprague and Edward F. Bland.
2. Antidiuresis in the Low-Sodium Syndrome in Congestive Failure. Drs. Alexander Leaf and Audley R. Mamby.
3. The Effect of Protoveratrine on Hypertensive Patients with Congestive Failure. Drs. Gordon S. Myers, Allan L. Friedlich, J. Gordon Scannell, James R. O'Neill, John F. McGinty and James H. Currens.

BOSTON CITY HOSPITAL — Dr. Laurence B. Ellis presiding

1. Intravenous Veriloid in the Management of Severe Hypertensive Disease. Dr. Norman S. Stearns.
2. Ventilatory Functions in Mitral Stenosis. Drs. Robert Frank, David W. Cugell, Edward A. Gaensler and Laurence B. Ellis.
3. Pharmacologic and Anticoagulant Properties of a Heparinoid Compound (Paritol) for Intramuscular Use. Drs. R. Zanca, T. Beatty, A. Donavan, J. Seifter, H. Sise and W. C. Moloney.

Interested physicians, medical students and members of the New England Postgraduate Assembly are cordially invited to attend.

EDWARD K. DUNHAM LECTURES

E. B. Verney, F.R.C.P., F.R.S., professor of pharmacology at the University of Cambridge, will deliver three lectures in the amphitheatre of Building D, Harvard Medical School, at 5 p.m., on the general subject "The Excretion of Water by the Kidney with Special Reference to Its Neurohypophysial Control." The dates and subjects of the lectures are as follows:

Tuesday, October 30. Glomerular Function and the Fate of the Filtrate Water.

Thursday, November 1. The Specific Excretion of Water and the Factors that Affect It.

Tuesday, November 6. The Osmotic Control of the Release of the Antidiuretic Hormones.

COMBINED ANESTHESIA TEACHING PROGRAM OF BOSTON

A program for the teaching of anesthesiology has been initiated as a co-operative effort of the Departments of Anesthesia of several Boston hospitals. Subject matter of the meetings includes the basic sciences, especially physiology and pharmacology as related to anesthesia, technics and methods of administration and specific problems in clinical management of patients. Sessions are held each Monday evening at the Stearns Auditorium of the New England Medical Center, 25 Bennet Street, 7-9 p.m. All physicians are invited to attend.

Departments of anesthesia participating in the program are the following:

Boston City Hospital (Dr. Sidney C. Wiggin, chief), Boston Lying-In Hospital (Dr. Bert B. Hershenson, chief), Children's Medical Center (Dr. Robert M. Smith, chief), Massachusetts Memorial Hospitals (Dr. Julia G. Arrowood, chief), New England Deaconess Hospital (Dr. Leo V. Hand, chief), New England Medical Center (Dr. Benjamin Etsten, chief), and Peter Bent Brigham Hospital (Dr. William S. Derrick, chief).

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association will present the following programs in its Evening Lecture Series:

October 30: "Recent Advances in the Study of the General-Adaptation Syndrome." Dr. Hans Selye, professor and director of the Institute of Experimental Medicine and Surgery, University of Montreal. Discussers: Dr. George W. Thorn and Dr. William Dameshek.

November 6: "Iron Metabolism and the Pathogenesis of Iron-Deficiency Anemia." Dr. Carl Moore, professor of medicine, Washington University School of Medicine. Discussers: Dr. Frank Gardner and Dr. Joseph F. Ross.

November 8: "Blood Substitutes and Their Use in the Treatment of Shock." Dr. James V. Warren, professor of physiology, Emory University School of Medicine. Discussers: Dr. John G. Gibson, II, and Dr. Arnold M. Seligman.

November 20: "Diabetic Acidosis." Dr. Edward Tolstoi, associate professor of clinical medicine, Cornell University Medical College. Discussers: Dr. Priscilla White, Dr. David Hurwitz and Dr. George Nichols.

November 27: "Periodic Disease." Dr. Hobart A. Reimann, professor of medicine, Jefferson Medical College. Discussers: Dr. Maxwell Finland and Dr. Chester S. Keefer.

These programs will be given at 7:00 p.m. in the New Cheever Amphitheatre of the Dowling Building of Boston City Hospital.

All interested persons are invited to attend.

ALPHA OMEGA ALPHA LECTURE

The Boston University Chapter of Alpha Omega Alpha will present a lecture on November 21 at 5:00 p.m., in the auditorium, Building A, 80 East Concord Street, Boston. Dr. Harry S. N. Greene, professor of pathology at Yale University School of Medicine, will speak on "The Significance of the Transplantability of Human Cancer."

All interested physicians are invited to attend.

MASSACHUSETTS DEPARTMENT OF MENTAL HEALTH POSTGRADUATE SEMINAR IN NEUROLOGY AND PSYCHIATRY

The sessions of the Review Course in Basic Neurology and Psychiatry of the Seventeenth Seminar in Neurology and Psychiatry, which began October 1, will be held every Monday, 2:00 p.m. to 8:30 p.m., until December 3, 1951, and from March 3 through May 5, 1952, at the Metropolitan State Hospital, 455 Trapelo Road, Waltham.

MEDICAL ASSOCIATION MEETINGS

Three medical associations will hold their meetings concurrently with the New England Postgraduate Assembly, which will take place at the Hotel Statler, November 7-9.

The New England Diabetes Association will hold a meeting at the New England Deaconess Hospital (Joslin Auditorium) on Tuesday, November 6, at 8:00 p.m. Dr. Russell M. Wilder of the National Institutes of Health, Washington, D. C., will speak on "Hypoglycemia."

The New England Rheumatism Association will hold its meeting at the New England Deaconess Hospital (Joslin Auditorium) on Thursday, November 8. The business meeting will open at 7:45 p.m., the society meeting at 8:00 p.m. Dr. Alexander B. Gutman, professor of medicine, Columbia University College of Physicians and Surgeons, will speak on "Uricosuric Agents in Chronic Tophaceous Gout."

The New England Cardiovascular Society will hold its meeting at the Dorothy Quincy Suite of John Hancock Hall, 180 Berkeley Street, Boston, on Thursday, November 8, at 8:00 p.m. Dr. Laurence B. Ellis and Dr. Edward F. Bland will preside. Staff members of the Boston City Hospital and the Massachusetts General Hospital will speak on current cardiovascular research.

AMERICAN UROLOGICAL ASSOCIATION ESSAY AWARDS

The American Urological Association offers an annual award of $1000 (first prize of $500, second prize $300 and third prize $200) for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been in such specific practice for not more than five years and to men in training to become urologists. Essays must be received before February 15, 1952.

The essay winning first prize will appear on the program of the forthcoming meeting of the American Urological Association, to be held at Chalfonte–Haddon Hall, Atlantic City, New Jersey, June 23-26, 1952.

Further information may be obtained from the Secretary, Dr. Charles H. de T. Shivers, Boardwalk National Arcade Building, Atlantic City, New Jersey.

POSITIONS AS MEDICAL OFFICER AT ST. ELIZABETH'S HOSPITAL

The United States Civil Service Commission has announced medical officers' examinations for the following positions in St. Elizabeth's Hospital, Washington, D. C.: rotating intern ($2200 a year); psychiatric resident ($3400 to $4200 a year); surgical resident ($4200 to $4700 a year); and general-practice resident ($3400 to $3800 a year).

To qualify for these positions, applicants must have had appropriate education in an approved medical school. Applicants for psychiatric, surgical and general-practice residencies must also have completed a one-year internship. In addition, applicants for surgical-resident appointments must have completed a two-year residency in surgery. No written tests are required. The maximum age limit is thirty-five years.

Persons who applied for but did not receive appointments under the Commission's 1950 examination for these positions should apply for this new examination.

Further information and application forms may be obtained from the United States Civil Service Commission, Washington 25, D. C., from Civil Service regional offices or from most first- and second-class post offices. Applications will be accepted until further notice by the Committee of United States Civil Service Examiners, St. Elizabeth's Hospital, Washington 25, D. C.

THE SPRINGFIELD HOSPITAL

The educational program of the Springfield Hospital for the month of November is as follows:

Saturday, November 3.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Microscopical Pathology Conference in the Staff Conference Room.
11 a.m.–12 m. Combined Medical-Surgical Grand Rounds in the Staff Conference Room.

Wednesday, November 7.
10 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

Thursday, November 8.
12:15 p.m. Staff Meeting in the Staff Room.

Saturday, November 10.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Surgical Conference in the Staff Conference Room.
11 a.m.–12 m. Clinicopathological Conference in the Staff Conference Room.

Wednesday, November 14.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

Saturday, November 17.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Urological Conference in the Staff Conference Room.
11 a.m.–12 m. Medical Death Review in the Staff Conference Room.

Tuesday, November 20.
8:30 p.m. Guest Speaker Conference in the Staff Conference Room on the subject "Practical Points in Transurethral Surgery." Dr. William A. Milner, associate professor of urology, Albany Medical College, and attending urologist, Albany Hospital, Albany, New York.

Wednesday, November 21.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

Saturday, November 24.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Surgical Conference in the Staff Conference Room.
11 a.m.–12 m. Medical Death Review in the Staff Conference Room.

Wednesday, November 28.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.
12 m.–2 p.m. Pediatric Conference in the Staff Conference Room.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 26. Research Conference. Dowling Amphitheatre, Boston City Hospital. 12:00 m.

OCTOBER 29. New York Institute of Clinical Oral Pathology. Page 628, issue of October 18.

OCTOBER 29. Beth Israel Hospital House Officers' Colloquium. Page 590, issue of October 11.

OCTOBER 29. Medicomilitary Symposium. Page 548, issue of October 4.

OCTOBER 29–NOVEMBER 2. American Public Health Association. Page 316, issue of August 23.

OCTOBER 30, NOVEMBER 1 AND 6. Edward K. Dunham Lectures. Page 669.

OCTOBER 30 AND NOVEMBER 6, 8, 20 AND 27. Boston City Hospital House Officers' Association. Page 669.

OCTOBER 31. Massachusetts Society of Examining Physicians. Page 668.

OCTOBER 31. New England Obstetrical and Gynecological Society, Hotel Somerset, Boston.

NOVEMBER 2 AND 3. Eastern Section, American Trudeau Society. Page 350, issue of August 30.

NOVEMBER 3–28. The Springfield Hospital. Notice above.

NOVEMBER 4 AND 5. American Society for the Study of Arteriosclerosis. Page xv, issue of July 12.

NOVEMBER 5. Beth Israel Hospital House Officers' Colloquium. Page 590, issue of October 11.

NOVEMBER 5–9. American College of Surgeons. Page 388, issue of September 6.

NOVEMBER 5, 19 AND 26. Beth Israel Hospital House Officers' Colloquium. Page 590, issue of October 11.

NOVEMBER 6. The New England Diabetes Association. Page 669.

NOVEMBER 7. Salmon Memorial Lecture. Page 548, issue of October 4.

NOVEMBER 7–9. New England Postgraduate Assembly. Hotel Statler, Boston. Program, page xiii, issue of October 11.

NOVEMBER 7–19. Pan-Pacific Surgical Association. Page 820, issue of May 24.

NOVEMBER 8. The New England Rheumatism Association. Notice above.

NOVEMBER 8. New England Cardiovascular Society. Page 669.

NOVEMBER 8. Diverticulitis — Conservative or Radical Management. Dr. Joseph Tartakoff. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

NOVEMBER 9. Rocky Mountain Harvard Medical School Alumni Association. Page 548, issue of October 4.

NOVEMBER 13. Springfield Academy of Medicine. Page 548, issue of October 4.

NOVEMBER 14. Salmon Memorial Lecture. Page 548, issue of October 4.

NOVEMBER 14. Northeastern New York Radiological Society. University Club, Albany, New York.

NOVEMBER 14 AND 15. Diabetes Fair. New England Diabetes Association. Page 669.

NOVEMBER 20. Salmon Memorial Lecture. Page 548, issue of October 4.

NOVEMBER 21. Alpha Omega Alpha Lecture. Page 669.

DECEMBER 2. American Academy of Dental Medicine. Page 548, issue of October 4.

DECEMBER 11–19. International Congress on Mental Health. Page xiii, issue of July 26.

DECEMBER 14 AND 15. Association for Research in Nervous and Mental Disease. Page 958, issue of June 21.

JANUARY 23, 1952. Suffolk District Medical Society. Page 669.

MAY 1–3, 1952. American Goiter Association. St. Louis, Missouri.

JULY 8–11, 1952. Thirteenth British Congress of Obstetrics and Gynaecology. Page xv, issue of December 14.

JULY 14–19, 1952. International Congress of Physical Medicine. Page 998, issue of June 28.

DISTRICT MEDICAL SOCIETIES

HAMPSHIRE

NOVEMBER 7. Northampton State Hospital, Northampton.
JANUARY 2. Veterans Hospital, Northampton.
MARCH 5. Cooley-Dickinson Hospital, Northampton.
MAY 7. Annual Meeting. Jones Library, Amherst.

(Notices concluded on page xvii)

Terramycin

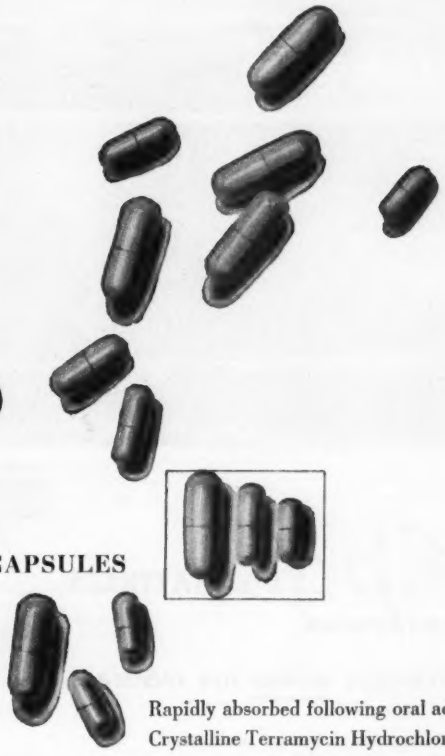

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Figure 1

on an ordinary mattress.

Hospital X-ray, 128-pound, 28-year old female, lying on her back on an ordinary mattress supported by a bedboard. Note that the spine and bone structure sink well below the horizontal top edge of the innerspring, with accompanying muscle strain.

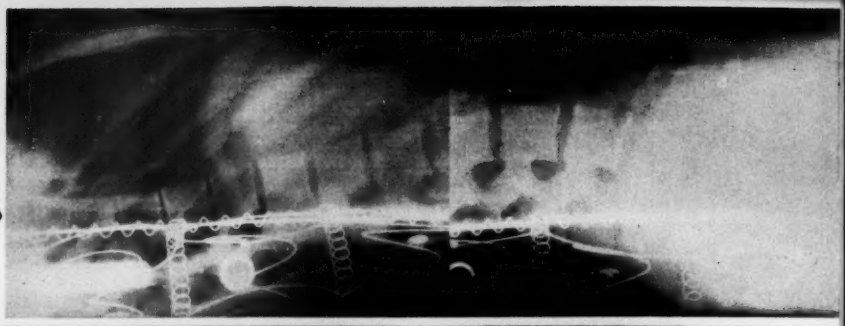


Figure 2

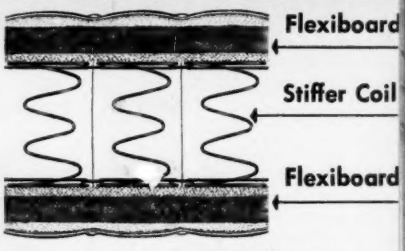
on Firmbak Flexiboard mattress.

Hospital X-ray, same 128-pound, 28-year old female as in Figure 1, lying on her back on the Firmbak Flexiboard mattress. Compare position of spine and bone structure with Figure 1. Support is provided by the mattress itself, permitting the muscles to rest.

Arrows indicate top of mattress.

THE Firmbak Flexiboard MATTRESS

for "bedboard" firmness *within* the mattress



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Developed through suggestions of many orthopedic physicians, the Firmbak Flexiboard mattress uses an entirely new construction principle to put bedboard firmness *within* the mattress — where it does the most good.

Its effectiveness is shown by the accompanying X-rays.

As seen in figure 1, the body sinks down into an ordinary mattress, *even* when a bedboard is used. Back muscles are in constant strain to maintain normal spinal contour.

On the Firmbak, the *mattress itself* supports the patient's body in proper sleeping posture, well above the top level of the innerspring. Muscles are relaxed and rested.

Firmbak's firm, level surface results from *built-in* dual Flexiboards — thick, firm, resilient cellulose posture pads, on both top and bottom of *stiffer* insulated innersprings. Layers of cotton felt are added for greater comfort.

For booklet, "Relieving Postural Backaches with the Firmbak Flexiboard Mattress", and for name of store in your city where patients can get Firmbak mattresses, write Rose-Derry Co., Newton 58, Mass.

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Tenth Annual New England Postgraduate Assembly

Sponsored by the Medical Societies of

MAINE, NEW HAMPSHIRE, VERMONT, MASSACHUSETTS, RHODE ISLAND AND CONNECTICUT

HOTEL STATLER, BOSTON—NOVEMBER 7-9

Program

WEDNESDAY, NOVEMBER 7

MORNING SESSION
Gastrointestinal Symposium

MOTION PICTURES

8:30 Gastrointestinal Cancer: The Problems of Early Diagnosis. American Cancer Society
Problems of Rheumatoid Arthritis. Arthritis and Rheumatism Foundation, Boston

CLINICS

9:30 Pancreatic Insufficiency
DRS. PERRY CULVER and PAUL PATTERSON
Complications of "Arrested" Cirrhosis
DRS. FRANZ J. INGELFINGER and JOSEPH FOLEY
10:30 Recess

LECTURES

10:50 Assembly called to order by the Chairman and DR. W. RICHARD OHLER, *President*, Massachusetts Medical Society
11:00 The Use of Antibiotics in Gastrointestinal Infections
DR. JOSEPH B. KIRSNER
11:30 Chronic Diarrheas DR. BENJAMIN V. WHITE

LUNCHEON PANELS

12:15 Disorders of the Bowel (Exclusive of Stomach and Rectum). Moderator: DR. SARA M. JORDAN; and DR. FRANZ J. INGELFINGER, DR. JOSEPH B. KIRSNER and DR. BENJAMIN V. WHITE
Newer Concepts of Medical Rehabilitation. Moderator: DR. AUGUSTUS THORNDIKE; and DR. HENRY H. KESSLER, DR. HEINRICH BRUGSCH, DR. ALEXANDER AITKEN, DR. ARTHUR L. WATKINS, MISS OTTILIE M. BANKS and DR. EDWARD D. CALLAHAN
2:00 Recess

AFTERNOON SESSION

LECTURES

2:30 Rehabilitation of the Injured DR. HENRY H. KESSLER
3:00 Blood Substitutes in Shock DR. JAMES V. WARREN
3:30 Recess
4:00 Some Applications of Industrial Toxicology in Medical Practice DR. ROBERT A. KEHOE
4:30 Some Practical Considerations of Diabetes
DR. RUSSELL M. WILDER

EVENING SESSION — JAMBOREE

8:15 The Doctor of Tomorrow and Federal Medical Services
DR. ROBERT C. PAGE, *Chairman*, National Doctor's Committee for Improved Federal Medical Services
9:00 Entertainment. FRED RONER, international pickpocket and humorist

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THURSDAY, NOVEMBER 8

MORNING SESSION
ACTH Symposium

MOTION PICTURES

8:30 Physiologic Basis of the Action of ACTH in Human Beings
Malnutrition in the Hospital Patient. E. R. Squibb & Sons

CLINICS

9:30 ACTH and Cortisone in Allergic States
DR. ROBERT P. MCCOMBS and associates
Peripheral Vascular Disease
DR. CLAUDE E. WELCH, DR. CHILTON CRANE, DR. GORDON DONALDSON and DR. JESSE THOMPSON
10:30 Recess

LECTURES

11:00 The Use of ACTH and Cortisone in Gastrointestinal Diseases
DR. JOSEPH B. KIRSNER
11:30 ACTH and Cortisone in Blood Diseases
DR. CARL MOORE

LUNCHEON PANELS

12:15 Endocrine Therapy. Moderator: DR. KENDALL EMERSON; and DR. SOMERS STURGIS, DR. THEODORE BAYLISS AND DR. ALBERT RENOLD
Gall-Bladder Disease. Moderator: DR. J. ENGLEBERT DUNPHY; DR. CHARLES G. MIXTER, DR. MERRILL C. SOSMAN and DR. S. ALLEN WILKINSON
2:00 Recess. Visit the Exhibits

AFTERNOON SESSION

LECTURES

2:30 Why Man Drinks DR. HAROLD W. LOVELL
3:00 Serious Medical Complications of Alcoholism
DR. MAURICE VICTOR and DR. RAYMOND D. ADAMS
3:30 Recess
4:00 The Treatment of Syphilis DR. HARRY EAGLE
4:30 Tobacco and Cancer of the Lung
DR. ERNEST L. WYNDER

FRIDAY, NOVEMBER 9

MORNING SESSION
Cardiovascular Symposium

MOTION PICTURES

8:30 The Heart — Electrokymography, Venous Catheterization and Angiocardiography G. D. Searle & Co.
Animated Hematology — Bone Marrow Armour & Co.
9:30 Diagnosis and Treatment of Paroxysmal Hypertension
DR. ROBERT W. WILKINS, DR. WILLIAM E. R. GREER and DR. REGINALD H. SMITHWICK
Disorders of the Spleen
DR. C. STUART WELCH, DR. WILLIAM DAMESHEK and associates
10:30 Recess

LECTURES

11:00 Newer Drugs in the Treatment of Hypertension
DR. HENRY A. SCHROEDER
11:30 Anticoagulants — Old and New
DR. EDGAR A. HINES, JR.

LUNCHEON PANELS

12:15 Cardiovascular Disease. Moderator: DR. SAMUEL A. LEVINE; and DR. EDWARD F. BLAND, DR. EDGAR A. HINES, DR. HENRY A. SCHROEDER and DR. B. F. MASSELL
The Acute Surgical Abdomen in Children. Moderator: DR. ORVAR SWENSON; and DR. JOHN DAVIES, DR. RICHARD SCHATZKI, DR. HENRY HUDSON and DR. BENJAMIN ETSTEN

The registration fee is $5.00 and should be forwarded by mail, if possible. There is no charge for the jamboree following the lecture. Dinner will be $3.00. Guests may be invited to the dinner and the jamboree if reservations are made in advance. Luncheons preceding the panels will be $2.00. Registrants may attend the panel discussions following the luncheons without charge.

Application blanks have been mailed to all physicians in New England. If you have not received one, please write to the New England Postgraduate Assembly, 8 Fenway, Boston 15.

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NOTICES (*Concluded from page 670*)

SUFFOLK

JANUARY 23. Massachusetts General Hospital.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 1

THURSDAY, NOVEMBER 1

*9:00-10:00 a.m. Grand Rounds. Robert Breck Brigham Hospital.
*9:00-10:00 a.m. Cardiac Grand Rounds. Main Amphitheatre, Children's Medical Center.
5:00 p.m. Edward K. Dunham Lecture. Amphitheatre, Building D, Harvard Medical School.

FRIDAY, NOVEMBER 2

*9:00 a.m.-12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.
*11:00 a.m.-1:00 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.
12:30-1:30 p.m. Tumor Conference. Pratt Lecture Hall, New England Center Hospital.
*1:30 p.m. Tumor Clinic. Outpatient Department, Mount Auburn Hospital, Cambridge.

MONDAY, NOVEMBER 5

*11:30 a.m.-12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:00 m.-1:00 p.m. Endocrine Conference. Dr. Astwood. Stearns Auditorium, New England Center Hospital.
*12:15-1:15 p.m. Clinicopathological Conference. Main Amphitheatre, Peter Bent Brigham Hospital.
2:00-8:30 p.m. Massachusetts Department of Mental Health Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital, Waltham.
*7:00-9:00 p.m. Combined Anesthesia Teaching Program of Boston. Stearns Auditorium, New England Center Hospital.
8:00 p.m. House Officers' Colloquium. Auditorium, Beth Israel Hospital.

TUESDAY, NOVEMBER 6

*12:00 m.-1:30 p.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*12:00 m.-1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15-1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
5:00 p.m. Edward K. Dunham Lecture. Amphitheatre, Building D, Harvard Medical School.
7:00 p.m. Boston City Hospital House Officers' Association. New Cheever Amphitheatre, Dowling Building.
8:00 p.m. New England Diabetes Association. New England Deaconess Hospital.

WEDNESDAY, NOVEMBER 7

*11:00 a.m.-12:00 m. Medical Clinic (Children's Medical Center). Amphitheatre, Children's Hospital.
*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Boston.
*12:00 m.-1:00 p.m. Clinicopathological Conference (Children's Medical Center). Amphitheatre, Peter Bent Brigham Hospital.
*12:00 m.-1:00 p.m. Neurology Conference. Dr. Raymond D. Adams. Stearns Auditorium, New England Center Hospital.
*12:00 m.-1:00 p.m. Medical Gynecology Conference. Dr. Joseph Rogers. Stearns Auditorium, New England Center Hospital.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheatre, New England Deaconess Hospital.
*2:00-3:00 p.m. Combined Clinic of All Services (Children's Medical Center). Amphitheatre, Children's Hospital.

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